Protocol Title	A Phase 2 Multicenter, Randomized, Double-Masked, Sham-Controlled Study of the Safety and Efficacy of Intravitreal Injections of NGM621 in Subjects with Geographic Atrophy (GA) Secondary to Age-Related Macular Degeneration (AMD) (CATALINA)
Name of Investigational Product	NGM621
Protocol Number	NGM621-GA-201
Sponsor Name/Contact	NGM Biopharmaceuticals, Inc. 333 Oyster Point Boulevard South San Francisco, CA 94080, USA Phone: PPD Fax: PPD
Sponsor Study Contact	PPD 333 Oyster Point Boulevard South San Francisco, CA 94080, USA Phone: PPD Fax:
Sponsor Medical Monitor Contact	PPD 333 Oyster Point Boulevard South San Francisco, CA 94080, USA Phone: PPD Fax:
Current Version – Date	Version 5.0 – 13 May 2021
Previous Versions – Date	Version 4.0 – 21 January 2021 Version 3.0 – 06 November 2020 Version 2.0 – 03 June 2020 Version 1.0 – 28 February 2020

SPONSOR PROTOCOL APPROVAL AND SIGNATURE PAGE

Protocol Title	A Phase 2 Multicenter, Randomized, Double-Masked, Sham-Controlled Study of the Safety and Efficacy of Intravitreal Injections of NGM621 in Subjects with Geographic Atrophy (GA) Secondary to Age-Related Macular Degeneration (AMD) (CATALINA)
Protocol Number	NGM621-GA-201
Name of Investigational Product	NGM621
Version #/ Date of Issue	Version 5.0 / 13 May 2021

I have read and approve the protocol specified above and agree on its content.

I agree to conduct the study as detailed herein and in compliance with ICH Guidelines for Good Clinical Practices and applicable regulatory requirements, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

NGM Biopharmaceuticals, Inc.,
Representatives:

PPD
Clinical Research

DocuSigned by:
PPD
PPD
Signature

5/14/2021
Date

INVESTIGATOR PROTOCOL APPROVAL AND SIGNATURE PAGE

Protocol Title	A Phase 2 Multicenter, Randomized, Double-Masked, Sham-Controlled Study of the Safety and Efficacy of Intravitreal Injections of NGM621 in Subjects with Geographic Atrophy (GA) Secondary to Age-Related Macular Degeneration (AMD) (CATALINA)
Protocol Number	NGM621-GA-201
Name of Investigational Product	NGM621
Version #/Date of Issue	Version 5.0 / 13 May 2021

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable best effort to complete the study within the time designated and will inform the company of any delays that could impair my ability to complete the study.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by NGM Biopharmaceuticals, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)	Signature
Date (DD MMM YYYY)	Site Number

PROTOCOL CHANGE HISTORY

This amendment is being done to increase the sample size of the study from 240 to 318 subjects; to modify the statistical testing procedure for the primary endpoint; to correct the schedule of study procedures to ensure consistency between tables and text; CCI [redacted] These updates are reflected in both the synopsis and main protocol.

Further details on the changes have been provided in the table below.

Location of Change	Change Made	Justification for Change
Synopsis; Section 5.1; Section 8.6	Sample size increased from 240 to 318 subjects (N=106 per arm for the NGM621 Q4wks, NGM621 Q8wks and the pooled sham arms)	Increasing the sample size to ensure adequate statistical power, providing outcomes that are more reliable and robust
Section 8.3.1.2	Modified statistical testing approach for primary endpoint from Hochberg to hierarchical testing sequence	Modified statistical approach is both rigorous and felt to be more appropriate for our study design
Section 3.3; Section 7.2.16; Section 7.2.17	CCI [redacted]	CCI [redacted]
Section 7.1; Section 7.2.12; Section 7.2.12.1	Pre- and post-dose IOP at Week 36 and Week 56 were changed to OU (both eyes)	Ensures consistency between tables and text
Section 7.1	Serum ADA and serum Nab sample collection were updated for the Q8 Week Arm at Week 8 in Table 5	Updated the table to match the text in Section 7.2

Table of Contents

Title Page....1
SPONSOR PROTOCOL APPROVAL AND SIGNATURE PAGE....2
INVESTIGATOR PROTOCOL APPROVAL AND SIGNATURE PAGE....3
PROTOCOL CHANGE HISTORY....4
Table of Contents....5
List of Tables....7
List of Appendices....8
List of Abbreviations....8
1 Synopsis....10
2 Introduction....28
2.1 Background....28
2.1.1 Geographic Atrophy (GA)....28
2.1.2 Mechanism of Action of NGM621....28
2.1.3 Therapeutic Rationale for NGM621 in Geographic Atrophy....29
2.1.4 Geographic Atrophy and Current Treatments....29
2.2 Summary of Nonclinical Studies....29
2.3 Summary of Clinical Studies....31
2.4 Rationale for Dose and Regimen Selection....34
3 Study Objectives and Endpoints....35
3.1 Primary Objectives and Endpoints....35
3.2 Secondary Objectives and Endpoints....35
3.3 Exploratory Objectives and Endpoints....36
4 Study Design....37
4.1 Methodology/ Study Design:....37
4.2 Study Stop Criteria....37
4.3 Data Safety Monitoring Board....38
5 Subject Selection....39
5.1 Inclusion Criteria....39
5.2 Exclusion Criteria....40
5.2.1 Ocular Exclusions....40
5.2.1.1 Study Eye....40
5.2.1.2 Both Eyes....41
5.2.1.3 Concurrent Ocular Conditions....41
5.2.1.4 Systematic Related....42
5.3 Comparison of Inclusion and Exclusion Criteria by Study Eye vs. Fellow Eye....42
5.4 Microperimetry (MP) Criteria (At Selected Sites Only)....44
5.4.1 MP Inclusion Criteria....44
5.4.2 MP Exclusion Criteria....44
6 Study Treatment....45
6.1 Clinical Supplies....45
6.1.1 NGM621....45
6.2 Administration/ Handling/ Storage/ Accountability....45
6.2.1 Administration....45
6.2.1.1 NGM621....45
6.2.1.2 Sham....45
6.2.2 Storage and Stability....45
6.2.3 Accountability....46
6.3 Randomization....46
6.3.1 Masking....46
6.3.2 Removal of Study Masking (If Applicable)....48
6.4 Concomitant Medications....48

6.5 Permitted Therapies 49
6.6 Lifestyle Considerations/Restrictions 49
6.7 Discontinuation of Subjects from Study Participation 49
7 Study Procedures 52
7.1 Schedule of Study Procedures 52
7.2 Study Visit Procedures 58
7.2.1 Screening (Day –28 to Day –3) Visit 58
7.2.2 Baseline (Day 1) Treatment Visit 59
7.2.3 Week 1 (± 3 days) Visit 60
7.2.4 Week 4 (± 5 days) Treatment Visit 60
7.2.5 Week 8 (± 5 days) Treatment Visit 61
7.2.6 Week 12 (± 5 days) Treatment Visit (Q4W Arms ONLY) 62
7.2.6.1 Week 12 (± 5 days) Telephone Safety Visit (Q8W Arms ONLY) 62
7.2.7 Week 16 (± 5 days) Treatment Visit 63
7.2.8 Week 20 (± 5 days) Treatment Visit (Q4W Arms ONLY) 63
7.2.8.1 Week 20 (± 5 days) Telephone Safety Visit (Q8W Arms ONLY) 64
7.2.9 Week 24 (± 5 days) Treatment Visit 64
7.2.10 Week 28 (± 5 days) Treatment Visit (Q4W Arms ONLY) 65
7.2.10.1 Week 28 (± 5 days) Telephone Safety Visit (Q8W Arms ONLY) 66
7.2.11 Week 32 (± 5 days) Treatment Visit 66
7.2.12 Week 36 (± 5 days) Treatment Visit (Q4W Arms ONLY) 67
7.2.12.1 Week 36 (± 5 days) Telephone Safety Visit (Q8W Arms ONLY) 67
7.2.13 Week 40 (± 5 days) Treatment Visit 67
7.2.14 Week 44 (± 5 days) Treatment Visit (Q4W Arms ONLY) 68
7.2.14.1 Week 44 (± 5 days) Telephone Safety Visit (Q8W Arms ONLY) 68
7.2.15 Week 48 (± 5 days) Treatment Visit 69
7.2.16 Week 52 (± 5 days) – End of Treatment (EOT) Visit (also Early Termination visit for any subjects that discontinue before week 52) 69
7.2.17 Week 56 (± 5 days) – Follow up and End of Study Visit 70
7.3 Study Assessments and Evaluations 71
7.3.1 Demographic/ Ocular Characteristics 71
7.3.2 Ocular/Medical and Surgical History 71
7.3.3 Body Weight 71
7.3.4 Vital Signs 71
7.3.5 Physical Examination 72
7.3.6 Clinical Laboratory Examinations 72
7.3.7 BCVA/LLVA 73
7.3.8 Reading Speed 74
7.3.8.1 The Minnesota Low-Vision Reading Test (MNRead) 74
7.3.8.2 Radner Reading Cards 74
7.3.9 FRI Index 74
7.3.10 NEI VFQ-25 74
7.3.11 Slit Lamp Biomicroscopy 74
7.3.12 Intraocular Pressure 75
7.3.12.1 Post Injection Assessment 75
7.3.13 Dilated Fundus Exam and Indirect Ophthalmoscopy 75
7.3.14 Ocular Imaging 76
7.3.14.1 SD-OCT 76
7.3.14.2 Fundus Autofluorescence 76
7.3.14.3 Color Fundus Photography (CFP) 76
7.3.14.4 Fluorescein Angiography (FA) 77
7.3.14.5 Microperimetry 77
7.3.15 Management of Choroidal Neovascularization (CNV) 77
7.3.15.1 Management of Choroidal Neovascularization (CNV)-Study Eye 77
7.3.15.2 Management of Choroidal Neovascularization (CNV)-Non-Study Eye 78
7.3.16 Clinical Genotyping Sample 78

7.4 Safety and Other Assessments 79
7.4.1 Adverse Events 79
7.4.1.1 Definition of Adverse Events 79
7.4.1.2 Definition of Serious Adverse Events and SAE Reporting 80
7.4.1.3 Classification of Severity of Adverse Event 81
7.4.1.4 Assessment of Causality of Adverse Events 81
7.4.1.5 Procedures for Recording Adverse Events 82
7.4.1.6 Diagnosis versus Signs and Symptoms 83
7.4.1.7 Adverse Events That Are Secondary to Other Events 83
7.4.1.8 Sight Threatening Event 84
8 Statistical Considerations 85
8.1 Analysis Sets 85
8.2 Demographics and Other Baseline Characteristics 85
8.3 Efficacy Analyses 85
8.3.1 Primary Efficacy Analyses 86
8.3.1.1 Primary Estimand 86
8.3.1.2 Main Estimation 86
8.3.1.3 Sensitivity Analyses 87
8.3.2 Secondary Efficacy Analyses 87
8.4 Safety Analyses 88
8.5 Pharmacokinetics Analyses 88
8.6 Sample Size Determination 88
9 Supporting Documentation and Operational Considerations 90
9.1 Regulatory, Ethical, and Study Oversight Considerations 90
9.1.1 Informed Consent Process 90
9.1.2 Ethics Committee 90
9.1.3 Protocol Adherence 90
9.1.4 Confidentiality and Privacy 90
9.1.5 Clinical Monitoring 91
9.1.6 Quality Assurance and Quality Control 91
9.1.7 Records 91
9.1.8 Financing and Insurance 92
9.1.9 Publication Policy 92
10 References 93
10.1 List of Sponsor's Clinical Studies Referenced in this Protocol 93
10.2 List of Sponsor's Nonclinical Studies Referenced in this Protocol 93
10.3 Literature References 93
11 Appendices 95
11.1 Grading Scale for Anterior Chamber Flare or Cells 95
11.2 Grading Scale for Vitreous Cells 95
11.3 Grading Scale for Vitreous Haze 96

List of Tables

Table 1. Study 18 0501: Frequency of Treatment Emergent Adverse Events (All Causalities) 32
Table 2. Study Design Study Design 37
Table 3. Dose -Interruption and Treatment Discontinuation Criteria 50
Table 4. Q4 Week Arms Schedule of Assessments (NGM621 and Sham) 53
Table 5. Q8 Week Arms Schedule of Assessments (NGM621 and Sham) 55
Table 6. Dosing Treatment Arms (NGM621 and Sham) 57
Table 7. Causal Attribution Guidance 82

List of Appendices

Appendix 1. Grading Scales 95

List of Abbreviations

Abbreviation	Definition/Explanation
Ab	Antibody
ADA	Anti-drug antibodies
ADL	Activities of daily living
AMD	Age-related macular degeneration
AE	Adverse event
AUC	Area under the curve
BCVA	Best corrected visual acuity
C3	Complement factor 3/ Complement component 3
CFP	Color Fundus Photography
CH50	Complement activity
CL/F	Clearance
C_{max}	Maximal concentration / Maximum observed serum concentration
CNV	Choroidal neovascularization
CRA	Clinical research associate
CRC	Central reading center
CRO	Clinical research organization
CTCAE	Common Terminology Criteria for Adverse Events
DME	Diabetic macular edema
DSMB	Data Safety Monitoring Board
EC	Ethics committee
eCRF	Electronic case report form
EOS	End of study
EOT	End of treatment
ERM	Epiretinal membrane
ETDRS	Early Treatment of Diabetic Retinopathy Study
FA	Fluorescein angiography
FAF	Fundus autofluorescence
FRI	Functional reading independence index
GA	Geographic Atrophy
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IHRF	Intraretinal hyperreflective foci
IO	Indirect ophthalmoscopy
IOP	Intraocular pressure
IRB	Institutional Review Board
IRT	Interactive response technology
IV	Intravenous
IVT	Intravitreal
LLD	Low luminance deficit
LLT	Lowest level term
LLVA	Low-luminance visual acuity
M	Million
MD	Multiple dose

MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat population
MMRM	Mixed-effect model for repeated measures
MP	Microperimetry
MTD	Maximum tolerated dose
NEI/SUN	National eye institute/ Standardization of uveitis nomenclature
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire 25-Item
NGM621	A humanized IgG1 monoclonal antibody that potently binds to human C3
NOAEL	No-observed-adverse-effect level
SD-OCT	Spectral Domain Optical coherence tomography
OU	Both eyes
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per protocol population
PRO	Patient reported outcome
Q4W	Every 4 weeks
Q8W	Every 8 weeks
RPD	Reticular pseudodrusen
RPE	Retinal pigment epithelium
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Study eye
SoA	Schedule of assessments
TEAE	Treatment emergent adverse event
$t_{1/2}$	Terminal half-life
V/F	Volume of distribution
VA	Visual acuity
VEGF	Vascular endothelial growth factor
YAG	Yttrium aluminum garnet

1 Synopsis

Study Title	A Phase 2 Multicenter, Randomized, Double-Masked, Sham-Controlled Study of the Safety and Efficacy of Intravitreal Injections of NGM621 in Subjects with Geographic Atrophy (GA) Secondary to Age-Related Macular Degeneration (AMD) (CATALINA)
Protocol Number	NGM621-GA-201
Phase	2
Sites	Approximately 75
Investigational Drug Product	NGM621 is a humanized monoclonal antibody against complement component factor 3 (C3).
Placebo	Sham injection
Indication	Geographic Atrophy (GA) secondary to age-related macular degeneration (AMD), hereafter referred to as GA.
Dose, Regimen, Mode	Subjects will be randomized to receive 15 mg of NGM621 or Sham administered by intravitreal (IVT) injection either every 4 weeks **or** every 8 weeks.
Primary Objectives and Endpoints:	The primary objectives of this study are to evaluate the efficacy and safety of NGM621 IVT injections administered every 4 or 8 weeks for a total of 52 weeks. • The primary efficacy endpoint is the rate of change in GA lesion area as measured by fundus autofluorescence (FAF) over 52 weeks of treatment. • The primary safety endpoints will evaluate the incidence and severity of ocular and systemic adverse events from treatment with NGM621 administered every 4 or 8 weeks compared to Sham.
Secondary Objectives and Endpoints	The secondary objectives of this study are to evaluate the 1) secondary efficacy 2) pharmacokinetics (PK) and 3) immunogenicity of NGM621 administered every 4 or 8 weeks in subjects with GA. The following endpoints will be measured: 1. Secondary Efficacy Endpoints: A. Change from baseline at Week 52 in: a. GA lesion area as assessed by FAF (mm^2/yr) b. Square root of GA lesion area assessed by FAF (mm)

c. BCVA score as assessed by ETDRS chart at a starting distance of 4 meters

d. LLVA score as assessed by ETDRS chart at a starting distance of 4 meters

e. Low Luminance Deficit (LLD; BCVA – LLVA) in ETDRS letters at a starting distance of 4 meters

f. Binocular reading speed by MNRead or Radner reading charts

g. Binocular critical print size as assessed by MNRead or Radner reading charts

h. Functional Reading Independence Index (FRI) composite score

i. NEI VFQ-25 composite score, near activity subscale score, distance activity subscale score

B. Change and percent change of systemic complement activity (CH50) from baseline at each visit

2. Secondary Pharmacokinetics Endpoint:

A. Serum trough concentration of NGM621

3. Secondary Immunogenicity Endpoint:

A. The incidence of anti-NGM621 antibodies (ADAs) in serum

Exploratory Objective and Endpoints:	CCI [redacted]

	CCI [redacted]
Inclusion Criteria	Subjects who meet the following criteria will be included in the study: 1. Male or female (non-pregnant, non-lactating) subjects ≥ 55 of age 2. Standard luminance BCVA score of 34 letters or better using ETDRS charts at the starting distance of 4 meters (approximately 20/200 Snellen equivalent or better) in study eye 3. Clinical diagnosis of GA secondary to AMD with the GA lesion meeting the following criteria as determined by the central reading center's assessment of Fundus Autofluorescence (FAF) imaging at screening: a) Total GA area must be ≥ 2.5 and ≤ 17.5 mm^2 b) If GA is multifocal, at least one focal lesion must be ≥ 1.25 mm^2 (0.5 DA), with the overall area of GA ≥ 2.5 and ≤ 17.5 mm^2 c) The entire GA lesion must be completely visualized on the macula centered image and must be able to be imaged in its entirety and not contiguous with any areas of peripapillary atrophy. d) Presence of banded or diffuse pattern of hyper-autofluorescence in the junctional zone of GA. Absence of hyper-autofluorescence in the junctional zone of the GA (i.e., pattern = none) is excluded. e) Well demarcated GA with no anatomical evidence (as assessed by FA and SD-OCT) of current or prior CNV in the study eye 4. Clear ocular media and adequate pupil dilatation and fixation in both eyes to permit good quality photographic imaging 5. Female subjects must be either of a) non-childbearing potential, defined as women who have had a hysterectomy, bilateral oophorectomy, medically documented ovarian failure, documented postmenopausal, or a follicle stimulating hormone > 40 mIU/mL, or b) if of childbearing potential, defined as women with < 2 years of amenorrhea (absence of menstruation), then must have a negative serum pregnancy test at Screening and urine pregnancy test at the Day 1 visit prior to first dose of study drug.

6. Female subjects of childbearing potential and male subjects with a female partner of childbearing potential must either be abstinent or be using consistent and adequate birth control from Screening to End of Study (EOS / Week 56). One of the following forms of contraception is required:

   a) Condom

   b) Hormone-containing contraceptive

   c) Intrauterine device with a failure rate < 1% per year

   d) Cervical cap or diaphragm with spermicidal agent

   e) Tubal sterilization

   f) Vasectomy in male partner

7. Willing and able to give informed consent, written local privacy requirements, comply with all visit procedures and likely to complete the study

Exclusion criteria

Ocular Exclusions

Study Eye

- History of prior intravitreal injection for neovascular AMD (see exception below), vitrectomy surgery, submacular surgery, or any surgical intervention for AMD. A single intravitreal injection of anti-VEGF, if administered > 2 years prior to screening, is permitted. A single intraoperative administration of a corticosteroid during cataract surgery for cystoid macular edema prophylaxis at least 3 months prior to screening is permitted.

- GA secondary to a condition other than AMD in either eye (e.g., monogenetic macular dystrophies like Stargardt disease, cone rod dystrophy, toxic maculopathies)

- Any history of or active choroidal neovascularization (CNV), based on fluorescein angiography (FA) and SD-OCT imaging as assessed by the Central Reading Center

- Previous laser photocoagulation for CNV, diabetic macular edema (DME), retinal vein occlusion and proliferative diabetic retinopathy

- Intraocular surgery (including lens replacement surgery) within 3 months prior to randomization

- History of laser therapy in the macular region

- Aphakia or absence of the posterior capsule. Note: yttrium aluminum garnet (YAG) laser posterior capsulotomy for posterior capsule opacification done at least 60 days prior to screening is not excluded.

- Any ocular condition other than GA secondary to AMD that may require surgery or medical intervention (including lens replacement surgery) during the study period or, in the opinion of the Investigator, could compromise visual function during the study period.

- Any contraindication to IVT injection including current ocular or periocular infection

- Autoimmune uveitis or scleritis, or chronic inflammatory disease of anterior segment, including chronic keratoconjunctivitis sicca (more than mild) or inflammatory blepharitis (noninfectious) of either eye (greater than mild severity), or chronic inflammatory disease of posterior chamber

Fellow (Non-study) Eye

- Any history of or active CNV less than 2 years in duration. CNV of greater than 2 years since clinical diagnosis is permitted for up to 25% of the total patient population. Permitted CNV can be receiving active treatment (e.g. anti-VEGF).

Both Eyes

- Any history of or active bacterial, viral, fungal, or parasitic infection in either eye in the 3 months prior to randomization

- Received any retinal stem cell treatment

- Previous participation in interventional clinical trials for GA or dry AMD, regardless of the route of administration (i.e., ocular or systemic) within the last 6 months of Day 1. Prior participation in vitamin and mineral clinical trials is allowed at any time prior to Day 1.

- Patients that received pegcetacoplan (also known as APL-2; Apellis) or avacincaptad pegol (also known as Zimura; Iveric Bio, formerly Ophthotech) in either eye are not eligible for participation.

Concurrent Ocular Conditions

- Retinal pigment epithelium (RPE) tear that involves the macula in either eye

- Presence of an active ocular disease in either or both eyes that in the opinion of the Investigator compromises or confounds visual function, including but not limited to, uveitis, other macular diseases (e.g., clinically significant epiretinal membrane [ERM], full thickness macular hole or uncontrolled glaucoma/ocular hypertension).

- History of idiopathic or autoimmune-associated uveitis in either eye
- Active, infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye
- Spherical equivalent of the refractive error in the study eye demonstrating > 8 diopters of myopia (determine axial length, exclude if axial length > 26 mm)
- Proliferative diabetic retinopathy or diabetic macular edema in either eye
- History of recurrent infectious or inflammatory ocular disease in either eye. Note: subjects with mild blepharitis will be allowed.

Systematic Related

- Clinically significant medical or psychiatric conditions that, in the opinion of the Investigator, make consistent follow-up over the 12-month treatment period unlikely, or would make the subject an unsafe study candidate.
- Any screening laboratory value (hematology, serum chemistry or urinalysis) that in the opinion of the Investigator is clinically significant and not suitable for study participation
- Presence or treatment for any active systemic or localized infection
- Known allergy to constituents of the study drug formulation or clinically relevant sensitivity to fluorescein
- Known significant history of drug/alcohol abuse or a positive drugs of abuse test at screening that could not be explained as appropriate management of a medical condition. (Cannabinoids are not part of drug screen)
- History severe allergic or anaphylactic reactions to recombinant therapeutic proteins, fusion proteins, or chimeric, human, or humanized antibodies
- History of malignancy diagnosed or treated within 2 years (recent localized treatment of squamous or non-invasive basal cell skin cancers is permitted; cervical carcinoma in situ or breast ductular carcinoma in situ is allowed if appropriately treated within 2 years prior to Screening); subjects under evaluation for malignancy are not eligible.

Microperimetry (MP) Criteria (At Selected Sites Only)

MP Inclusion Criteria

Microperimetry screening test criteria for eligibility:

- Must be able to detect fixation target

- Total elapsed time to complete the 10-2 68-point exam is ≤ 30 minutes in duration
- Reliability Test ratio ≤ 20% (false positive rate)
- Ability and willingness to undertake MP assessment as determined by Investigator

MP Exclusion Criteria

- Investigator determines that subject is unable to perform the rest reliably. Note: disqualification from the microperimetry assessment does not exclude a subject from the trial participation if she/he qualifies as per the rest of the study entry criteria.

Comparison of Inclusion and Exclusion Criteria by Study Eye vs. Fellow Eye

Criterion	Study Eye	Fellow Eye
Inclusion Criteria / Ocular Conditions:		
• Standard luminance BCVA score of 34 letters or better using ETDRS charts at the starting distance of 4 meters (approximately 20/200 Snellen equivalent or better) in the study eye	✓	
• Clinical diagnosis of GA secondary to AMD with the GA lesion meeting the following criteria as determined by the central reading center's assessment of Fundus Autofluorescence (FAF) imaging at screening: a) Total GA area must be ≥ 2.5 and ≤ 17.5 mm^2 b) If GA is multifocal, at least one focal lesion must be ≥ 1.25 mm^2 (0.5 DA), with the overall area of GA ≥ 2.5 and ≤ 17.5 mm^2 c) The entire GA lesion must be completely visualized on the macula centered image and must be able to be imaged in its entirety and not contiguous with any areas of peripapillary atrophy d) Presence of banded or diffuse pattern of hyper-autofluorescence in the junctional zone of GA. Absence of hyper-autofluorescence in the junctional zone of the GA (i.e., pattern = none) is excluded e) Well demarcated GA with no anatomical evidence (as assessed by FA and SDOCT) of current or prior CNV	✓	
• Clear ocular media and adequate pupil dilatation and fixation to permit good quality photographic imaging.	✓	✓
Exclusion Criteria / Ocular Conditions		
• History of prior intravitreal injection for neovascular AMD (see exception below); a single intravitreal injection of anti-VEGF, if administered > 2 years prior to screening, is permitted. A single intraoperative administration of a corticosteroid during cataract surgery for cystoid macular edema prophylaxis at least 3 months prior to screening is permitted.	✓	

• GA secondary to a condition other than AMD in either eye (e.g., monogenetic macular dystrophies like Stargardt disease, cone rod dystrophy, toxic maculopathies).	✓	
• Any history of or active choroidal neovascularization (CNV), based on fluorescein angiography (FA) and SD-OCT imaging as assessed by the Central Reading Center	✓	
• Previous laser photocoagulation for CNV, diabetic macular edema (DME), retinal vein occlusion, and proliferative diabetic retinopathy.	✓	
• Intraocular surgery (including lens replacement surgery) within 3 months prior to randomization.	✓	
• History of laser therapy in the macular region.	✓	
• Aphakia or absence of the posterior capsule. Note: yttrium aluminum garnet (YAG) laser posterior capsulotomy for posterior capsule opacification done at least 60 days prior to screening is not excluded.	✓	
• Any ocular condition other than GA secondary to AMD that may require surgery or medical intervention (including lens replacement surgery) during the study period or, in the opinion of the Investigator, could compromise visual function during the study period.	✓	
• Any contraindication to IVT injection including current ocular or periocular infection.	✓	
• Autoimmune uveitis or scleritis, or chronic inflammatory disease of anterior segment, including chronic keratoconjunctivitis sicca (more than mild) or inflammatory blepharitis (noninfectious) of either eye (greater than mild severity), or chronic inflammatory disease of posterior chamber.	✓	✓
• Any history of or active CNV < 2 years in duration. CNV of > 2 years since clinical diagnosis is permitted for up to 25% of the total patient population. Permitted CNV can be receiving active treatment (e.g., anti-VEGF).		✓
• Any history of or active bacterial, viral, fungal, or parasitic infection in the 3 months prior to randomization	✓	✓
• Received any retinal stem cell treatment.	✓	✓
• Previous participation in interventional clinical trials for GA or dry AMD, regardless of the route of administration (i.e., ocular or systemic) within the last 6 months of Day 1. Prior participation in vitamin and mineral clinical trials is allowed at any time prior to Day 1.	✓	✓
• Patients that received pegcetacoplan (also known as APL2; Apellis) or avacincaptad pegol (also known as Zimura; Iveric Bio, formerly Ophthotech) in either eye are not eligible for participation.	✓	✓

Exclusion Criteria / Concurrent Ocular Conditions:		
• Retinal pigment epithelium (RPE) tear that involves the macula	✓	✓
• Presence of an active ocular disease that in the opinion of the Investigator compromises or confounds visual function, including but not limited to, uveitis, other macular diseases (e.g., clinically significant epiretinal membrane (ERM), full thickness macular hole or uncontrolled glaucoma/ocular hypertension).	✓	✓
• History of idiopathic or autoimmune-associated uveitis	✓	✓
• Active, infectious conjunctivitis, keratitis, scleritis, or endophthalmitis	✓	✓
• Spherical equivalent of the refractive error in the study eye demonstrating >8 diopters of myopia (determine axial length, exclude if axial length > 26 mm).	✓	
• Proliferative diabetic retinopathy or diabetic macular edema	✓	✓
• History of recurrent infectious or inflammatory ocular disease. Note: subjects with mild blepharitis will be allowed.	✓	✓

Study Design/ Methodology:

This is a Phase 2 randomized, double-masked, sham-controlled, multicenter study of the safety and efficacy of intravitreal injections of NGM621 in subjects with GA secondary to AMD in one or both eyes. Only one eye can be chosen as the study eye. In the event both eyes are eligible, the eye with the worse visual function (lower BCVA value) will be considered for the purpose of this study as the study eye. If both eyes have the same visual function, the eye with the larger area of GA will be selected as the study eye. In the event that both eyes have the same visual function and GA area, the right eye will be selected.

Approximately 318 subjects, screened within 4 weeks prior to dosing, who have signed the informed consent and meet all eligibility criteria, will be assigned randomly to 1 of 4 treatment groups in a ratio of 2:1:2:1 to receive IVT injections of 15 mg of NGM621 (100 µL volume) or Sham, every 4 weeks or every 8 weeks for a total of 52 weeks (see Study Design table below and protocol Table 6). Subjects will be monitored for 56 weeks, and the total duration of individual participation (including screening time) will be approximately 60 weeks. Subjects who discontinue before completion of 52 weeks of treatment may be replaced. Mesopic microperimetry of the study eye only will be performed at select study sites. For additional details please refer to Section 7.3.14.5 of the protocol.

Study Design:

Treatment Group	Study Treatment	Treatment Regimen Module	Number of Subjects Planned
A	15 mg NGM621 (100 µL)	Every 4 weeks	106
B	Sham	Every 4 weeks	53
C	15 mg NGM621 (100 µL)	Every 8 weeks	106
D	Sham	Every 8 weeks	53
Total Number of Study Subjects Planned			318

Schedule of Assessments / Q4 Week Arms (NGM621 and Sham)

Study flowchart for Q4W Arms: Day 1, Week 1, Week 4 through Week 56

Activity/ Assessment	Screen	Baseline	Treatment														Follow Up
	Day -28 to Day -3	Day 1	Wk 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52 EOT [9]	Wk 56 EOS
Month				M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14
Visit Windows			±3	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
Informed Consent	X																
Inclusion/ Exclusion criteria	X																
Demographics	X															X	
Ocular/Medical History	X																
Physical Exam	X															X	
Body Weight	X															X	
Pregnancy Testing [1]	X	X														X	
Blood Sample (Hematology, chemistry) [2]	X															X	
Urine Sample (Urinalysis, Drug Screen)	X																
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X								X							X	X
FRI Index [3]		X							X							X	
NEI VFQ-25 [3]		X							X							X	
BCVA	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU
LLVA	OU								OU							OU	
Reading Speed		X							X							X	
Pre- and Post-dose IOP [4]	OU	OU	SE	SE	SE	OU	SE	SE	OU	SE	SE	OU	SE	SE	SE	OU	OU

Slit lamp Biomicroscopy	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU
Dilated Fundus Exam and Indirect Ophthalmoscopy	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU
SD-OCT [5]	OU						OU		OU		OU		OU			OU	OU
Fundus Autofluorescence (FAF) [6]	OU								OU							OU	
Fluorescein angiography (FA) [5]	OU																
Color Fundus Photography (CFP)	OU															OU	
Microperimetry at select sites (Study eye only) [7]	SE	SE							SE							SE	
Serum PK [8]		X	X	X			X		X				X		X	X	X
Serum ADA [8]		X		X			X		X				X		X	X	X
Serum NAb [8]		X		X			X		X				X		X	X	X
Serum – C3 and CH50		X	X	X					X							X	X
CCI [redacted]																	
Randomization		X															
Optional Buccal Swab for genetic testing[10]		*One-time collection at any visit from Day 1 to EOS. Collect only if subject has consented to optional procedure.*															
Dosing (Please see Table 6)																	

OU = both eyes; SE = study eye; X= Required

[1] Females of childbearing potential only; Serum pregnancy test to be conducted at screening. Urine pregnancy test to be conducted on Day 1 and Week 48 visit. If pregnancy is suspected, a serum pregnancy test may be conducted.
[2] For the screening visit only, it is allowable to draw blood in the order of assessments as listed in the table OR the blood draw can occur right before the FA assessment to allow for a single needle stick.
[3] The patient-reported outcome (PRO) measures (NEI VFQ-25 and FRI Index) will be administered by the masked site staff (except for the VA examiner) prior to any other visit assessments being performed.
[4] Reference Section 7.3.12.1 and the pharmacy manual for details.

[5] A FA and SD-OCT should be performed if the development of CNV is suspected in study eye. The central reading center must confirm this finding before any intervention is initiated. See Section 7.3.15 for details.
[6] After randomization, if a patient misses a study visit when FAF images were scheduled to be taken, the images should be taken at the next scheduled visit.
[7] Microperimetry is optional and applies to select sites.
[8] PK, Anti-drug antibody and neutralizing antibody samples will be collected at Day 1 pre-dose, Week 1 post-dose (PK collection only), Weeks 4, 16, 24, 44, 48 pre--dose, and on Weeks 52 and 56.
[9] For subjects who discontinue early from the study, the EOT visit assessments should be performed after a minimum of 28 days has elapsed from the last administered dose. See Section 6.7 for details.
[10] For subjects who consented to the optional sample collection.

Schedule of Assessments / Q8 Week Arms (NGM621 and Sham)

Study flowchart for Q8W Arms: Day 1, Week 1, Week 4 through Week 56

	Screen	Baseline	Treatment														Follow Up
Activity/Assessment	**Day -28 to Day -3**	**Day 1**	**Wk 1**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52 EOT[10]**	**Wk56 EOS**
Month				**M1**	**M2**		**M4**		**M6**		**M8**		**M10**		**M12**	**M13**	**M14**
Visit Windows			**±3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**
Informed Consent	X																
Inclusion/ Exclusion criteria	X																
Demographics	X															X	
Ocular/Medical History	X																
Physical Exam	X															X	
Body Weight	X															X	
Pregnancy Testing [1]	X	X														X	
Blood Sample (Hematology, chemistry) [2]	X															X	
Urine Sample (Urinalysis, Drug Screen)	X																
Adverse Events [3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X								X							X	X
FRI Index [4]		X							X							X	
NEI VFQ-25 [4]		X							X							X	
BCVA	OU	OU	OU	OU	OU		OU		OU		OU		OU		OU	OU	OU
LLVA	OU								OU							OU	
Reading Speed		X							X							X	
Pre- and Post-dose IOP [5]	OU	OU	SE		SE		SE		OU		SE		SE		SE	OU	OU
Slit lamp Biomicroscopy	OU	OU	OU	OU	OU		OU		OU		OU		OU		OU	OU	OU
Dilated Fundus Exam and Indirect Ophthalmoscopy	OU	OU	OU	OU	OU		OU		OU		OU		OU		OU	OU	OU
SD-OCT [6]	OU						OU		OU		OU		OU			OU	OU
Fundus Autofluorescence (FAF) [7]	OU								OU							OU	
Fluorescein angiography (FA) [6]	OU																
Color Fundus Photography (CFP)	OU															OU	
Microperimetry at select sites (Study eye only) [8]	SE	SE							SE							SE	
Serum PK [9]		X	X	X	X		X		X				X		X	X	X
Serum ADA [9]		X		X	X		X		X				X		X	X	X
Serum NAb [9]		X		X	X		X		X				X		X	X	X
Serum – C3 and CH50		X	X	X					X							X	X
CCI [redacted]																	
Randomization		X															

Optional Buccal Swab for genetic testing[11]		*One-time collection at any visit from Day 1 to EOS. Collect only if subject has consented to optional procedure.*
Dosing (please see Table 6)		

OU = both eyes; SE = study eye; X= Required

[1] Females of childbearing potential only; Serum pregnancy test to be conducted at screening. Urine pregnancy test to be conducted on Day 1 and Week 48 visit. If pregnancy is suspected, a serum pregnancy test may be conducted.
[2] For the screening visit only, it is allowable to draw blood in the order of assessments as listed in the table OR the blood draw can occur right before the FA assessment to allow for a single needle stick.
[3] Columns shaded gray indicate that adverse event reporting will be by telephone ( ) for non-visit months (Weeks 12, 20, 28, 36, and 44) for subjects in the Q8W arm only.
[4] The patient-reported outcome (PRO) measures (NEI VFQ-25 and FRI Index) will be administered by the masked site staff (except for the VA examiner) prior to any other visit assessments being performed.
[5] Reference Section 7.3.12.1 and the pharmacy manual for details.
[6] A FA and SD-OCT should be performed if the development of CNV is suspected in study eye. The central reading center must confirm this finding before any intervention is initiated. See Section 7.3.15 for details.
[7] After randomization, if a patient misses a study visit when FAF images were scheduled to be taken, the images should be taken at the next scheduled visit.
[8] Microperimetry is optional and applies to select sites.
[9] PK, Anti-drug antibody and neutralizing antibody samples will be collected Day 1 pre-dose, Week 1 post-dose (PK collection only), Week 4 post-dose, Weeks 8, 16, 24, 40, 48 pre-dose, and Weeks 52 and 56.
[10] For subjects who discontinue early from the study, the EOT visit assessments should be performed after a minimum of 28 days has elapsed from the last administered dose. See Section 6.7 for details.

[11] For subjects who consented to the optional sample collection.

Schedule of Assessments / Dosing Treatment Arms

	Screen	**Baseline**	**Treatment**														**Follow Up**
Treatment Arm	**Day -28 to Day -3**	**Day 1**	**Wk 1**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52 EOT**	**Wk 56 EOS**
NGM621 15 mg Q4W		X[1]		X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]		
Sham Q4W		X[1]		X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]		
NGM621 15 mg Q8W		X[1]			X[1]		X[1]		X[1]		X[1]		X[1]		X[1]		
Sham Q8W		X[1]			X[1]		X[1]		X[1]		X[1]		X[1]		X[1]		

[1] Refer to Section 7.3.12.1 and the pharmacy manual for details on treatment administration and pre- and post-dose IOP monitoring, and if needed, IOP management instructions.

Statistical Methods

Analysis Sets

- Modified Intent-To-Treat (mITT) Analysis Set: All randomized and treated (with at least one dose of study drug) subjects. This analysis set will be used for all efficacy analyses and subjects will be analyzed based on the treatment group into which they are randomized.
- Per Protocol (PP) Analysis Set: A subset of subjects in the mITT Analysis Set who have no protocol deviations that affect the GA lesion assessments (by FAF). This analysis set will be used for sensitivity analyses to support the mITT analyses.
- Safety Analysis Set: All treated subjects. This analysis set will be used for all safety analyses and subjects will be analyzed based on the actual treatment they receive.
- Pharmacokinetic (PK) Analysis Set: A subset of subjects in the Safety Analysis Set who have quantifiable PK measurements post first dose. This analysis set will be used for all PK analyses and subjects will be analyzed based on the actual treatment they receive.

General Statistical Considerations

In general, descriptive statistics including the number of non-missing observations (n), arithmetic mean (mean), standard deviation (SD), median, minimum (min), and maximum (max) will be presented by treatment group for continuous variables. Frequency and percentage distribution will be presented by treatment group for categorical variables.

Primary Efficacy Analyses

Primary Estimand

The estimand for the primary interest of this study is defined as follows:

1. Treatment: NGM621 Q4W, NGM621 Q8W, and pooled Sham (Sham injections Q4W or Q8W).
2. Population: subjects with geographic atrophy secondary to age-related macular degeneration as defined by the inclusion-exclusion criteria of the study.
3. Endpoint: rate of change in GA lesion area as measured by FAF over the 52 weeks of treatment.
4. Inter-current events and their corresponding strategies: see Section 8.3.1.1.

5. Population-level summary: the treatment group difference between each NGM621 group and the pooled Sham group in the mean change from baseline to Week 52 in the GA lesion area as measured by FAF.

Main Estimation

The GA lesion area (at baseline, Week 24, and Week 52) will be analyzed using a random coefficients model. The model includes terms for time (continuous variable assuming linearity) and treatment-by-time interaction. The intercept and slope of time are assumed to be random effects with a bivariate normal distribution and an unstructured (UN) covariance matrix while the treatment-by-time interaction is assumed to be a fixed effect. If there is a convergence issue under the assumed covariance structure (UN) for the random effect, then a variance-components covariance structure will be used. The within-subject errors are assumed to be independent and identically distributed normal random variables and are assumed to be independent of the random intercept and random slope. Within the framework of this model, a point estimate of the treatment group difference in the regression slope between each NGM621 group and the pooled Sham group will be provided. The corresponding two-sided 95% confidence interval and p-value for the point estimate will also be presented.

A hierarchical testing procedure will be used to control the family-wise type-I error rate associated with the tests of the two NGM621 groups (NGM621 Q4W vs pooled Sham and NGM621 Q8W vs pooled Sham). Specifically, the comparison between NGM621 Q4W and pooled Sham will be performed first. If this test is statistically significant at the 5% level, then the comparison between NGM621 Q8W and pooled Sham will be performed. If the first test is not statistically significant at the 5% level, then the comparison between NGM621 Q8W and pooled Sham will be considered exploratory.

Sensitivity Analyses

Sensitivity analyses will be performed to assess the robustness of the main estimator of the primary estimand. These sensitivity analyses will be performed with missing data imputed by the multiple imputation approach using the Markov Chain Monte Carlo (MCMC) method, a placebo-based pattern mixture model, and a tipping point method, respectively. The details of these analyses will be provided in the statistical analysis plan (SAP).

In addition, a sensitivity analysis will be performed using a nonlinear mixed effects model. In this model, the intercept is assumed to be a normal random variable, and the mean GA lesion area is assumed to be an exponential function of time with a separate slope (of time) for each treatment group. The within-subject errors are assumed to be independent and identically distributed normal random

variables and are assumed to be independent of the random intercept. The details of this analysis will be provided in the SAP.

Secondary Efficacy Analyses

Secondary efficacy endpoints include change from baseline at Week 52 in GA lesion area, the square root of GA lesion area, BCVA score, LLVA letter score, LLD in EDTRS letters at a starting distance of 4 meters, binocular reading speed (by MNRead or Radner reading charts), binocular critical print size (by MNRead or Radner reading charts), FRI composite score, and NEI VFQ-25, as well as change and percent change of CH50 from baseline. The change from baseline will be analyzed using a linear mixed-effects model. The model includes fixed effects for treatment, visit, treatment-by-visit interaction, and the baseline outcome value as a covariate. The covariance structure for this model will be assumed to be unstructured. If the model does not converge under this assumption, then a compound symmetry covariance structure will be used. Within the framework of this model, a point estimate of the treatment group difference at Week 52 between each NGM621 group and the pooled Sham group will be provided. The corresponding two-sided 95% confidence interval and p-value for the point estimate will also be presented.

Safety Analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Ocular and systemic treatment-emergent adverse events (TEAEs) will be summarized by primary system organ class and preferred term. Actual values and change from baseline values for vital signs, clinical laboratory (hematology and chemistry) tests and other continuous variables (both ocular and non-ocular) will be summarized with descriptive statistics. Concomitant medications, physical examinations, and other categorical (safety) variables (both ocular and non-ocular) will be summarized with frequency and percentage distribution. All safety analyses will be performed using the Safety Analysis Set.

Pharmacokinetics Analyses

Individual and mean serum NGM621 concentration–time data will be tabulated and plotted by cohort/dose level.

CCI [redacted]

Additional PK analyses and/or summary statistics will be conducted as appropriate.

2 Introduction

2.1 Background

2.1.1 Geographic Atrophy (GA)

Age-related macular degeneration (AMD) is a leading cause of blindness in the United States and the developed world. It is estimated that ~196 million (M) people have AMD globally and expected to increase to 288M by 2040 (Wong 2014). Approximately 15.7M have late stage disease, and this number is expected to increase to 26M by 2040 (Wong 2014). There are two advanced forms of AMD: the neovascular/exudative form, also referred to as wet AMD, and the atrophic form, called geographic atrophy (GA). While neovascular AMD tends to cause more rapid and severe vision loss, it can be managed with one of several approved intravitreal (IVT) anti-VEGF therapies. GA causes more gradual, but relentlessly progressive and irreversible vision loss. It was previously estimated that GA accounted for one-tenth of the blindness due to AMD, while neovascular AMD accounted for the remainder (Ferris 1984). Due to the advent of anti-VEGF therapy, recent studies have reported that GA accounts for approximately one-quarter of legal blindness in the United Kingdom and the United States (Holz 2014, Boyer 2017). An effective therapy for GA is one of the most important unmet needs in all of ophthalmology.

2.1.2 Mechanism of Action of NGM621

NGM621 is a humanized IgG1 antibody that potently (0.34 nM KD) inhibits human complement component 3 (C3), and thus functionally inhibits classical and alternative complement proteins. Specifically, NGM621 inhibits the enzymatic cleavage of C3 by C3 convertase. The C3a and C3b release products lead to downstream activation of the complement cascade to mediate immune cell response as well as opsonization activity (van Lookeren Campagne 2007). Moreover, C3b may also lead to further activation of the C3 convertase to propagate the complement activation response (Sahu 2001). NGM621 is only cross-reactive to cynomolgus monkey C3 with comparable binding affinity and in vitro activity to that of human C3. NGM621 has been engineered with point mutations in the Fc region that reduce binding to Fcγ receptors.

NGM621 is being developed for geographic atrophy (GA) secondary to age-related macular degeneration (AMD). The predominant genetic risk factors in AMD, including GA, implicate a dysregulation of the complement pathway that is critically important in immune/inflammatory responses (Kandasamy 2017, Danis 2015). Genome-wide association studies have identified polymorphisms in a number of complement proteins (CFH, C2, CFB, C3, C7, CFI) associated with AMD, and preclinical data suggest that genetic variants in complement factors leads to an overall low-grade activation of the complement system in the eye that may lead to the pathophysiology of AMD. Given the potential role of complement

activation in the pathogenesis of GA, NGM621 treatment in the eye may reduce the inflammation and tissue damage associated with complement activation, and, thus, reduce the rate of retinal tissue damage/atrophy.

2.1.3 Therapeutic Rationale for NGM621 in Geographic Atrophy

Dysregulation of the complement system is a contributing factor to the pathophysiology of the disease (Kandasamy 2017) due to several genetic polymorphisms associated with GA secondary to AMD. Multiple clinical investigations are exploring the effect of inhibition of various components of the complement system on GA. These include inhibiting Factor D of the alternative pathway with lampalizumab, which failed in late-stage clinical development; inhibiting the C5 component of the late complement system, which has produced conflicting results; and inhibiting the C3 component of the complement system. C5 clinical trials have included intravenous (IV) eculizumab (Alexion Pharmaceuticals), which did not decrease the growth rate of GA (NCT00935883); LFG316 (Novartis), which was terminated for futility (Yehoshua 2014, NCT01527500); and Zimura™ (avacincaptad pegol; Iveric Bio (formerly Ophthotech)), which did reduce GA growth in a recently completed Phase 3 study (NCT02686658). Pegcetacoplan (previously APL-2; Apellis Pharmaceuticals), a C3-targeted inhibitor, also reported a significant reduction in the growth of GA lesion size in a Phase 2 study of (NCT02503332). However, both avacincaptad pegol and APL-2 are pegylated and are associated with an increase in the incidence of CNV in subjects (Singh 2018, IVERIC press release 2019), confirming observations from rodent models of CNV that suggest that pegylation may lead to increased vascular leakage (Park 2019).

NGM621, a C3 cleavage inhibitor, may offer an efficacy as well as safety advantage over these leading candidates in clinical development, given its potency in inhibiting cleavage of C3 and its absence of pegylation.

2.1.4 Geographic Atrophy and Current Treatments

There is no currently approved treatment for GA.

2.2 Summary of Nonclinical Studies

The pharmacology, pharmacokinetics, and safety profile of NGM621 are detailed in the current version of the NGM621 Investigator's Brochure (IB).

In vitro functional activity assays have demonstrated the ability of NGM621 to inhibit both the cleavage of C3 to C3a and the complement-mediated hemolysis in cynomolgus monkey and human sera. In cynomolgus monkeys, NGM621 demonstrated pharmacological activity following IV or IVT administration at high doses due to its ability to inhibit complement-mediated hemolysis.

The pharmacokinetic (PK) profile of NGM621 was evaluated in the rabbit and the cynomolgus monkey following IVT and/or IV administration. NGM621 exposure in ocular tissues increased in a dose-dependent manner; $t_{1/2}$ of NGM621 ranged from approximately 3.0 to 3.5 days in ocular tissue. NGM621 was also measurable in serum following IVT injection with a PK profile consistent for a monoclonal antibody. In the cynomolgus monkey, the systemic $t_{1/2}$ of NGM621 was approximately 10 days following IV or IVT injection. There was no meaningful accumulation of NGM621 after repeat once monthly IVT dosing in the cynomolgus monkey. Overall, the pharmacokinetic (PK) properties observed for NGM621 in the cynomolgus monkey were consistent with those expected for a humanized IgG1 antibody. The ocular pharmacokinetic and pharmacodynamic (PKPD) profile of NGM621 in cynomolgus monkeys following IVT injection supports every 4- and 8-week dosing regimens.

The nonclinical safety of NGM621 was assessed in the cynomolgus monkey for up to 28 weeks of repeat dosing with a 12-week treatment-free period. The cynomolgus monkey was the only relevant species in which to assess the nonclinical safety of NGM621 based on pharmacologic activity of the molecule.

NGM621 was well tolerated in cynomolgus monkeys up to the highest dose tested (12.1 mg/eye) when administered once every 4 weeks by IVT injection for 28 weeks (seven doses total) (Study NGM621-TX-04). NGM621 produced no effect on clinical pathology and urine chemistry parameters up to 28 weeks of treatment. NGM621 had no effect on safety pharmacology parameters (body temperature, cardiovascular endpoints, respiration rate, and blood gas parameters) when evaluated in the 5-week monkey toxicology study. There were no ocular clinical signals that were considered related to NGM621 administration, with the exception of bilateral ocular inflammation noted in one animal dosed at 12.1 mg/eye. This change was considered secondary to the development of an ADA-mediated immunogenicity response and not relevant to human safety. No meaningful changes in intraocular pressure were attributed to NGM621 treatment.

At 28 weeks, there were no NGM621-related effects on organ weight or on macroscopic or microscopic evaluation of systemic tissues or the eye following IVT injection. No evidence for systemic C3 inhibition was noted following IVT injection up to the highest dose tested. NGM621 was also well tolerated following IV (9 mg/kg) administration, where higher systemic exposure was achieved, and no systemic effects were noted.

Based on the cumulative nonclinical safety profile of NGM621 for up to 28 weeks of treatment in the cynomolgus monkey, the no-observed-adverse-effect level (NOAEL) was determined to be 12.1 mg/eye, the maximal feasible IVT dose. The exposure margins in the eye at the NOAEL were ~1.6-fold above the proposed dose of 15 mg/eye. The exposure margins for systemic exposure (serum $AUC_{0–28d}$) of approximately 27-fold exist between the NOAEL in animal toxicity studies relative to the 15 mg/eye dose.

2.3 Summary of Clinical Studies

NGM conducted a Phase 1 (Study 18-0501) first-in-human multicenter, open label, single-dose and multiple-dose escalation study of the safety, tolerability, and pharmacokinetics of IVT injections of NGM621 in subjects with geography atrophy secondary to age-related macular degeneration.

A total of 9 subjects (3 subjects per dose) were dosed with either 2, 7.5, or 15 mg NGM621 by IVT injection in the single ascending dose (SAD) portion of the study, and 6 subjects were dosed twice (separated by 4 weeks) with 15 mg NGM621 in the multi-dose (MD) portion of the study. All 15 subjects completed the 12-week follow-up.

NGM621 was well tolerated when administered as a single IVT dose of 2, 7.5, or 15 mg and as multiple IVT doses of 15 mg (two doses 4 weeks apart). The number of subjects reporting TEAEs was similar for each dose level in the SAD cohorts and for the MD cohort. Overall, 9 subjects (60.0%) had 14 TEAEs including 4 subjects (26.7%) that had ocular TEAEs. No dose-related trend in the number of subjects reporting treatment emergent adverse events (TEAEs) was observed. No TEAEs were SAEs or considered by the Investigator to be related to NGM621 administration, and the majority of TEAEs were mild in severity. No TEAEs were serious or lead to study withdrawal (Table 1).

Table 1. Study 18 0501: Frequency of Treatment Emergent Adverse Events (All Causalities)

MedDRA SOC Preferred term	Treatment: SAD Cohorts 2 mg NGM621 (N = 3)	SAD Cohorts 7.5 mg NGM621 (N = 3)	SAD Cohorts 15 mg NGM621 (N = 3)	MD Cohort 15 mg NGM621 (N = 6)	Overall (N = 15)
Cardiac disorders	0	0	1 (33.3) [1]	0	1 (6.7) [1]
Ventricular extrasystoles	0	0	1 (33.3) [1]	0	1 (6.7) [1]
Eye disorders	0	1 (33.3) [1]	0	3 (50.0) [4]	4 (26.7) [5]
Conjunctival haemorrhage	0	0	0	2 (33.3) [3]	2 (13.3) [3]
Eye pruritus	0	1 (33.3) [1]	0	1 (16.7) [1]	2 (13.3) [2]
Gastrointestinal disorders	0	1 (33.3) [1]	0	0	1 (6.7) [1]
Diarrhoea	0	1 (33.3) [1]	0	0	1 (6.7) [1]
Infections and infestations	1 (33.3) [1]	1 (33.3) [1]	0	0	2 (13.3) [2]
Diverticulitis	0	1 (33.3) [1]	0	0	1 (6.7) [1]
Pneumonia	1 (33.3) [1]	0	0	0	1 (6.7) [1]
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	1 (33.3) [1]	0	0	0	1 (6.7) [1]
Basal cell carcinoma	1 (33.3) [1]	0	0	0	1 (6.7) [1]
Nervous system disorders	0	0	1 (33.3) [1]	1 (16.7) [2]	2 (13.3) [3]
Headache	0	0	0	1 (16.7) [1]	1 (6.7) [1]
Hypoaesthesia	0	0	0	1 (16.7) [1]	1 (6.7) [1]
Sciatica	0	0	1 (33.3) [1]	0	1 (6.7) [1]
Reproductive system and breast disorders	1 (33.3) [1]	0	0	0	1 (6.7) [1]
Benign prostatic hyperplasia	1 (33.3) [1]	0	0	0	1 (6.7) [1]

( ) = percentage of subjects with adverse events; [ ] = number of adverse events. .

Overall, ocular safety was favorable. Mild ocular TEAEs of conjunctival hemorrhage and eye pruritus were each experienced by 2 subjects. Conjunctival hemorrhages were likely due to the injection procedure and resolved on their own and the 2 cases of eye pruritus were resolved with artificial tears. No subjects experienced endophthalmitis, ocular inflammation, or CNV in either eye over the 12-week follow-up period.

No vision-related safety signals were detected. No clinically significant slit-lamp biomicroscopy findings were reported from baseline to the end of study following examination of eye lids/lashes, cornea, iris, lens, and optic nerve for both eyes for all subjects. As expected in GA subjects, there were clinically significant findings for the macula examination reported at screening/baseline but there was no clinically significant ophthalmoscopy findings post-baseline through the end of the study following the vitreous, peripheral retina, and choroid examination of both eyes.

At dose levels where the dose volume was 100 µL (2 and 15 mg NGM621) the majority of subjects had transient increases in IOP at 15 minutes post-injection. Three patients had IOP recordings of 25 or 26 mmHg at the 15-minute post-injection IOP but the pressure returned to the normal range by 60 minutes post-injection. Overall, minimal impact to pre-dose IOP was observed from baseline to 12 weeks.

Evaluating efficacy was unfeasible due to the short time window, small sample size, and absence of control. The study eye GA lesions, as assessed by FAF, were generally stable over the 12-week follow-up period for individual subjects on each treatment. Center point thickness and total retinal volume were similar over the 12-week follow-up period in the study eye. The BCVA assessment (ETDRS BCVA) was used for safety purposes.
On average subjects maintained or improved their visual acuity over the 12-week follow-up.

No safety concerns were noted during the study based on clinical laboratory evaluations, vital signs, 12-lead ECGs, and physical examinations. No safety patterns or concerns were identified that would preclude further investigation of NGM621.

Serum PK samples were obtained at predetermined timepoints out to 84 days post-dose. The serum PK of NGM621 following IVT injection was linear and dose-proportional with low accumulation ratio following every 4week repeat dosing. Following a single and repeat IVT administration, NGM621 exhibited slow systemic absorption with the median T_{max} of between 7.05 and 13.95 days. The mean CL/F was between 232.05 and 275.59 mL/day and the mean terminal half-life was between 12.27 and 14.89 days. There was a dose-proportional increase in NGM621 across the 2 to 15 mg dose range, based on C_{max} and $AUC_{0–inf}$. Following the repeat IVT dose of 15 mg every 4 weeks, the accumulation ratio was 1.50 and 1.61 based on C_{max} and AUC, respectively.

Following IVT administration of NGM621 serum exposure was below concentrations that produce systemic complement inhibition. Additionally, all subjects were antidrug antibody (ADA) negative at baseline and all follow-up timepoints through the 12-week study duration.

For additional details regarding nonclinical and clinical studies, see the NGM621 Investigator's Brochure.

2.4 Rationale for Dose and Regimen Selection

The NGM621 dose and dose regimen is based on the safety and tolerability of NGM621 in Phase 1 Study 18-0501 as well as the pharmacokinetic and pharmacodynamic (PKPD) profile of NGM621. The 15 mg monthly (Q4W) dosage was the maximum evaluated dosing regimen in Phase 1 Study 18-0501. PKPD simulations incorporating both C3 target engagement and inhibition potency demonstrated that both Q4W and Q8W dosing frequencies will result in a desirable range of reduction in C3 and inhibition of its activity following a 15 mg IVT injection. Although the extent of C3 target engagement required for clinical efficacy is unknown, it is anticipated that the dose and dose regimen selected would be sufficient for activity. Thus, the NGM621 dose of 15 mg was selected for IVT administration at Q4W or Q8W intervals to provide dose ranging data and inform optimal dosing frequency for future studies. The 15 mg administered Q8W is expected to achieve lower systemic drug exposures relative to 15 mg Q4W while maintaining effective concentrations for activity in ocular target tissues. Additionally, the Q8W dosing regimen represents less of a treatment burden to subjects, caregivers, and physicians relative to a Q4W dosing regimen.

3 Study Objectives and Endpoints

3.1 Primary Objectives and Endpoints

The primary objectives of this study are to evaluate the efficacy and safety of NGM621 intravitreal (IVT) injections administered every 4 or 8 weeks for a total of 52 weeks.

- The primary efficacy endpoint is the rate of change in GA lesion area as measured by fundus autofluorescence (FAF) over the 52 weeks of treatment.
- The primary safety endpoints will evaluate the incidence and severity of ocular and systemic adverse events from treatment with NGM621 administered every 4 or 8 weeks compared to Sham.

3.2 Secondary Objectives and Endpoints

The secondary objectives of this study are to evaluate the 1) secondary efficacy, 2) pharmacokinetics (PK), and 3) immunogenicity of NGM621 administered every 4 or 8 weeks in subjects with GA.

The following endpoints will be measured:

1. Secondary Efficacy Endpoints:

   A. Change from baseline at Week 52 in:

      a. GA lesion area as assessed by FAF (mm^2/yr)

      b. The square root of GA lesion area (mm)

      c. BCVA score as assessed by ETDRS chart at a starting distance of 4 meters

      d. LLVA score as assessed by ETDRS chart at a starting distance of 4 meters

      e. Low Luminance Deficit (LLD; BCVA – LLVA) in ETDRS letters at a starting distance of 4 meters

      f. Binocular reading speed by MNRead or Radner reading charts

      g. Binocular critical print size as assessed by MNRead or Radner reading charts

h. Functional Reading Independence Index (FRI) composite score

i. NEI VFQ-25 composite score, near activity subscale score, distance activity subscale score

B. Change and percent change of systemic complement activity (CH50) from baseline at each visit.

2. Secondary Pharmacokinetics Endpoint:

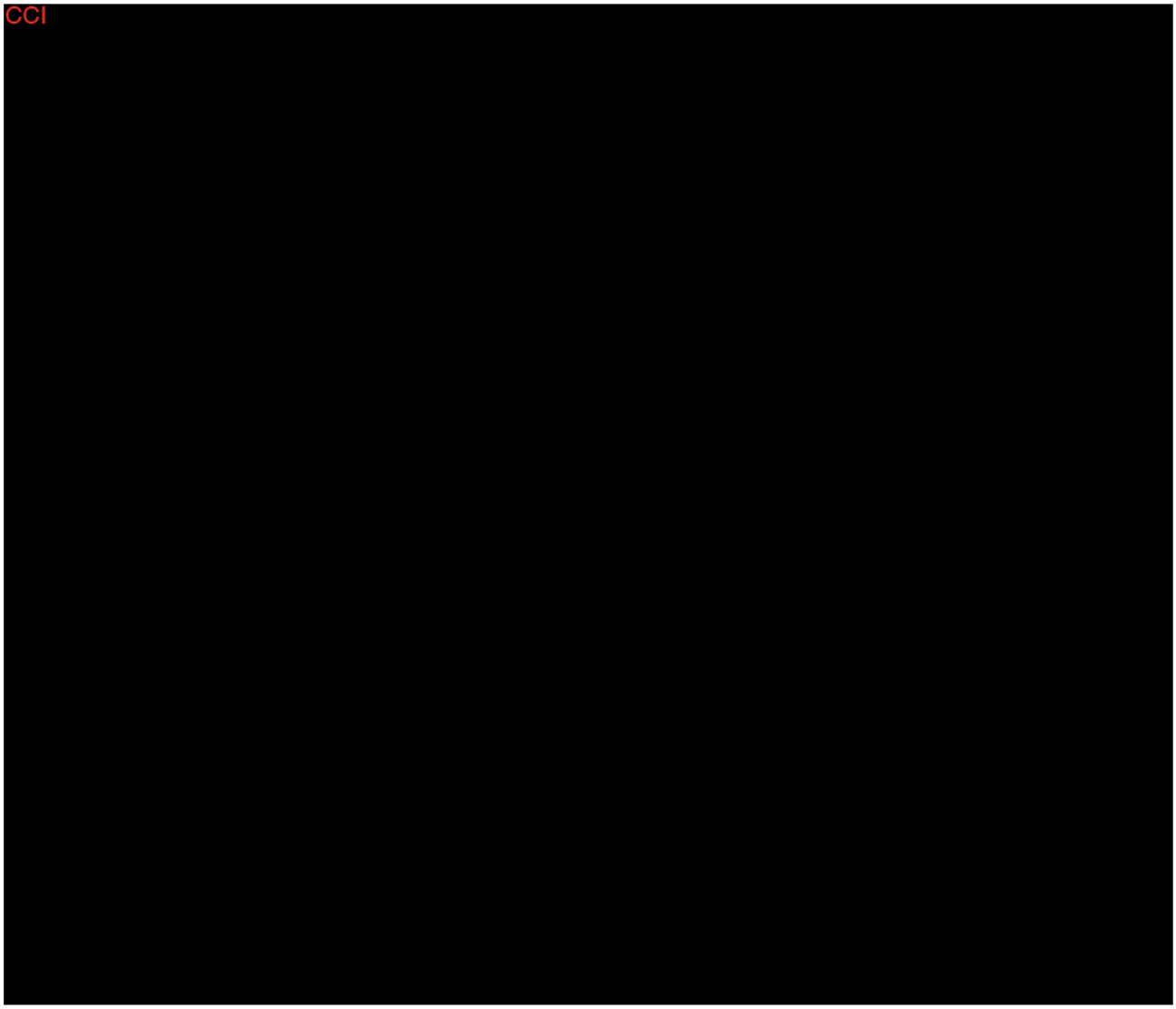
A. Serum trough concentration of NGM621

3. Secondary Immunogenicity Endpoint:

A. The incidence of anti-NGM621 antibodies (ADAs) in serum

3.3 Exploratory Objectives and Endpoints

CCI



4 Study Design

4.1 Methodology/ Study Design:

This is a Phase 2 randomized, double-masked, Sham-controlled, multicenter study of the safety and efficacy of IVT injections of NGM621 in subjects with GA secondary to AMD in one or both eyes. Only one eye can be chosen as the study eye. In the event both eyes are eligible, the eye with the worse visual function (lower BCVA value) will be considered for the purpose of this study as the study eye. If both eyes have the same visual function, the eye with the larger area of GA will be selected as the study eye. In the event that both eyes have the same visual function and GA area, the right eye will be selected.

Approximately 318 subjects, screened within 4 weeks prior to dosing, who have signed the informed consent and meet all eligibility criteria, will be assigned randomly to 1 of 4 treatment groups in a ratio of 2:1:2:1 to receive IVT injections of 15 mg of NGM621 (100 µL volume) or Sham, every 4 weeks or every 8 weeks for a total of 52 weeks (Table 2). Subjects will be monitored for 56 weeks, and the total duration of individual participation (including screening time) will be approximately 60 weeks. Subjects who discontinue before completion of 52 weeks of treatment may be replaced. Mesopic microperimetry of the study eye only will be performed at select study sites. For additional details please refer to Section 7.3.14.5.

Table 2. Study Design Study Design

Treatment Group	Study Treatment	Treatment Regimen Module	Number of Subjects Planned
A	15 mg NGM621 (100 µL)	Every 4 weeks	106
B	Sham	Every 4 weeks	53
C	15 mg NGM621 (100 µL)	Every 8 weeks	106
D	Sham	Every 8 weeks	53
Total Number of Study Subjects Planned			318

4.2 Study Stop Criteria

The entire study may be discontinued at the discretion of the Sponsor based on the occurrence of the following:

- AEs with respect to their frequency, severity, and/or duration;
- Medical or ethical reasons affecting the continued performance of the study;
- Difficulties in the recruitment of subjects; and/or
- Cancellation of drug development

4.3 Data Safety Monitoring Board

An independent Data and Safety Monitoring Board (DMSB) monitors safety and study conduct on an ongoing basis. The DSMB will be established under a separate charter, which will detail the roles/responsibilities and function of the DSMB. Members of the DSMB are external to the Sponsor and will consist of at least 2 or more independent physicians. The DSMB will meet approximately every 6 months (and ad hoc as needed). The DSMB will be provided data that are summarized by treatment arm using masked treatment arm labels (i.e., A, B, C). After reviewing the data by masked treatment arm, the DSMB may request to review unmasked data if deemed necessary to assess the benefit–risk profile of NGM621.

The DSMB will make recommendations to the Sponsor regarding further conduct of the study (i.e. continue as designed, continue with minor or major modifications, or study termination). No formal efficacy or futility analysis is planned for the study. The Sponsor will remain masked to all data transfers provided to the DSMB (see Section 6.3.1 for information about unmasking for SAEs).

5 Subject Selection

5.1 Inclusion Criteria

Subjects who meet the following criteria will be included in the study:

1. Male or female (non-pregnant, non-lactating) subjects ≥ 55 of age

2. Standard luminance BCVA score of 34 letters or better using ETDRS charts at the starting distance of 4 meters (approximately 20/200 Snellen equivalent or better) in study eye

3. Clinical diagnosis of GA secondary to AMD with the GA lesion meeting the following criteria as determined by the central reading center's assessment of Fundus Autofluorescence (FAF) imaging at screening:

   a) Total GA area must be ≥ 2.5 and ≤ 17.5 mm^2

   b) If GA is multifocal, at least one focal lesion must be ≥ 1.25 mm^2 (0.5 DA), with the overall area of GA ≥ 2.5 and ≤ 17.5 mm^2

   c) The entire GA lesion must be completely visualized on the macula-centered image and must be able to be imaged in its entirety and not contiguous with any areas of peripapillary atrophy.

   d) Presence of banded or diffuse pattern of hyper-autofluorescence in the junctional zone of GA. Absence of hyper-autofluorescence in the junctional zone of the GA (i.e., pattern = none) is excluded.

   e) Well demarcated GA with no anatomical evidence (as assessed by FA and SD-OCT) of current or prior CNV in the study eye

4. Clear ocular media and adequate pupil dilatation and fixation in both eyes to permit good quality photographic imaging

5. Female subjects must be either of a) non-childbearing potential, defined as women who have had a hysterectomy, bilateral oophorectomy, medically documented ovarian failure, documented postmenopausal, or a follicle stimulating hormone > 40 mIU/mL, or b) if of childbearing potential, defined as women with < 2 years of amenorrhea (absence of menstruation), then must have a negative serum pregnancy test at Screening and urine pregnancy test at the Day 1 visit prior to first dose of study drug.

6. Female subjects of childbearing potential and male subjects with a female partner of childbearing potential must either be abstinent or be using consistent and adequate birth control from Screening to End of Study (EOS / Week 56). One of the following forms of contraception is required:

a) Condom

b) Hormone-containing contraceptive

c) Intrauterine device with a failure rate < 1% per year

d) Cervical cap or diaphragm with spermicidal agent

e) Tubal sterilization

f) Vasectomy in male partner

7. Willing and able to give informed consent, written local privacy requirements, comply with all visit procedures and likely to complete the study

5.2 Exclusion Criteria

Subjects will be excluded if they meet the following criteria:

5.2.1 Ocular Exclusions

5.2.1.1 Study Eye

1. History of prior IVT injection for neovascular AMD (see exception below), vitrectomy surgery, submacular surgery, or any surgical intervention for AMD. A single IVT injection of anti-VEGF, if administered > 2 years prior to screening, is permitted. A single intraoperative administration of a corticosteroid during cataract surgery for cystoid macular edema prophylaxis at least 3 months prior to screening is permitted.

2. GA secondary to a condition other than AMD in either eye (e.g., monogenetic macular dystrophies like Stargardt disease, cone rod dystrophy, or toxic maculopathies).

3. Any history of or active choroidal neovascularization (CNV), based on fluorescein angiography (FA) and SD-OCT imaging as assessed by the Central Reading Center.

4. Previous laser photocoagulation for CNV, diabetic macular edema (DME), retinal vein occlusion and proliferative diabetic retinopathy.

5. Intraocular surgery (including lens replacement surgery) within 3 months prior to randomization.

6. History of laser therapy in the macular region.

7. Aphakia or absence of the posterior capsule. Note: yttrium aluminum garnet (YAG) laser posterior capsulotomy for posterior capsule opacification done at least 60 days prior to screening is not excluded.

8. Any ocular condition other than GA secondary to AMD that may require surgery or medical intervention (including lens replacement surgery) during the study period or, in the opinion of the Investigator, could compromise visual function during the study period.

9. Any contraindication to IVT injection including current ocular or periocular infection.

10. Autoimmune uveitis or scleritis, or chronic inflammatory disease of anterior segment, including chronic keratoconjunctivitis sicca (more than mild) or inflammatory blepharitis (noninfectious) of either eye (greater than mild severity), or chronic inflammatory disease of posterior chamber.

5.2.1.2 Fellow (Non-study) Eye

11. Any history of or active choroidal neovascularization (CNV) less than 2 years in duration. CNV of greater than 2 years since clinical diagnosis is permitted for up to 25% of the total patient population. Permitted CNV can be receiving active treatment (e.g., anti-VEGF).

5.2.1.2 Both Eyes

12. Any history of or active bacterial, viral, fungal, or parasitic infection in either eye in the 3 months prior to randomization.

13. Received any retinal stem cell treatment.

14. Previous participation in interventional clinical trials for GA or dry AMD, regardless of the route of administration (i.e., ocular or systemic) within the last 6 months of Day 1. Prior participation in vitamin and mineral clinical trials is allowed at any time prior to Day 1.

15. Patients who received pegcetacoplan (also known as APL2; Apellis) or avacincaptad pegol (also known as Zimura; Iveric Bio, formerly Ophthotech) in either eye are not eligible for participation.

5.2.1.3 Concurrent Ocular Conditions

16. Retinal pigment epithelium (RPE) tear that involves the macula in either eye.

17. Presence of an active ocular disease in either or both eyes that in the opinion of the Investigator compromises or confounds visual function, including but not limited to, uveitis, other macular diseases (e.g., clinically significant epiretinal membrane (ERM), full thickness macular hole or uncontrolled glaucoma/ocular hypertension).

18. History of idiopathic or autoimmune-associated uveitis in either eye.

19. Active, infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye.

20. Spherical equivalent of the refractive error in the study eye demonstrating > 8 diopters of myopia (determine axial length, exclude if axial length > 26 mm).

21. Proliferative diabetic retinopathy or diabetic macular edema in either eye.

22. History of recurrent infectious or inflammatory ocular disease in either eye.
Note: subjects with mild blepharitis will be allowed.

5.2.1.4 Systematic Related

23. Clinically significant medical or psychiatric conditions that, in the opinion of the Investigator, make consistent follow-up over the 12-month treatment period unlikely, or would make the subject an unsafe study candidate.

24. Any screening laboratory value (hematology, serum chemistry or urinalysis) that in the opinion of the Investigator is clinically significant and not suitable for study participation.

25. Presence or treatment for any active systemic or localized infection.

26. Known allergy to constituents of the study drug formulation or clinically relevant sensitivity to fluorescein.

27. Known significant history of drug/alcohol abuse or a positive drugs of abuse test at screening that could not be explained as appropriate management of a medical condition. (Cannabinoids are not part of drug screen).

28. History severe allergic or anaphylactic reactions to recombinant therapeutic proteins, fusion proteins, or chimeric, human, or humanized antibodies.

29. History of malignancy diagnosed or treated within 2 years (recent localized treatment of squamous or non-invasive basal cell skin cancers is permitted; cervical carcinoma in situ or breast ductular carcinoma in situ is allowed if appropriately treated within 2 years prior to Screening); subjects under evaluation for malignancy are not eligible.

5.3 Comparison of Inclusion and Exclusion Criteria by Study Eye vs. Fellow Eye

Criterion	Study Eye	Fellow Eye
Inclusion Criteria / Ocular Conditions:		
• Standard luminance BCVA score of 34 letters or better using ETDRS charts at the starting distance of 4 meters (approximately 20/200 Snellen equivalent or better) in the study eye	✓	
• Well-demarcated GA with no anatomical evidence (as assessed by FA and SD-OCT) of current or prior CNV	✓	
• Clear ocular media and adequate pupil dilatation and fixation to permit good quality photographic imaging.	✓	✓

	Exclusion Criteria / Ocular Conditions		
•	History of prior IVT injection, vitrectomy surgery, submacular surgery, or any surgical intervention for AMD. A single IVT injection of anti-VEGF, if administered greater than 2 years prior to screening, is permitted. A single intraoperative administration of a corticosteroid during cataract surgery for cystoid macular edema prophylaxis at least 3 months prior to screening is permitted.	✓	
•	GA secondary to a condition other than AMD in either eye (e.g., monogenetic macular dystrophies like Stargardt disease, cone rod dystrophy, toxic maculopathies).	✓	
•	Any history of or active choroidal neovascularization (CNV), based on fluorescein angiography (FA) and SD-OCT imaging as assessed by the Central Reading Center	✓	
•	Previous laser photocoagulation for CNV, diabetic macular edema (DME), retinal vein occlusion and proliferative diabetic retinopathy.	✓	
•	Intraocular surgery (including lens replacement surgery) within 3 months prior to randomization.	✓	
•	History of laser therapy in the macular region.	✓	
•	Aphakia or absence of the posterior capsule. Note: yttrium aluminum garnet (YAG) laser posterior capsulotomy for posterior capsule opacification done at least 60 days prior to screening is not excluded.	✓	
•	Any ocular condition other than GA secondary to AMD that may require surgery or medical intervention (including lens replacement surgery) during the study period or, in the opinion of the Investigator, could compromise visual function during the study period.	✓	
•	Any contraindication to IVT injection including current ocular or periocular infection.	✓	
•	Autoimmune uveitis or scleritis, or chronic inflammatory disease of anterior segment, including chronic keratoconjunctivitis sicca (more than mild) or inflammatory blepharitis (noninfectious) of either eye (greater than mild severity), or chronic inflammatory disease of posterior chamber.	✓	✓
•	Any history of or active CNV less than 2 years in duration. CNV of > 2 years since clinical diagnosis is permitted for up to 25% of the total patient population. Permitted CNV can be receiving active treatment (e.g., anti-VEGF).		✓
•	Any history of or active bacterial, viral, fungal, or parasitic infection in the 3 months prior to randomization	✓	✓
•	Received any retinal stem cell treatment.		
•	Previous participation in interventional clinical trials for GA or dry AMD, except for vitamins and minerals, regardless of the route of administration (i.e., ocular or systemic) within the last 6 months of Day 1.	✓	✓
Exclusion Criteria / Concurrent Ocular Conditions:			
•	Retinal pigment epithelium (RPE) tear that involves the macula	✓	✓
•	Presence of an active ocular disease that in the opinion of the Investigator compromises or confounds visual function, including but not limited to, uveitis, other macular diseases (e.g., clinically significant epiretinal membrane (ERM), full thickness macular hole or uncontrolled glaucoma/ocular hypertension).	✓	✓
•	History of idiopathic or autoimmune-associated uveitis	✓	✓
•	Active, infectious conjunctivitis, keratitis, scleritis, or endophthalmitis	✓	✓
•	Spherical equivalent of the refractive error in the study eye demonstrating > 8 diopters of myopia (determine axial length, exclude if axial length > 26 mm).	✓	
•	Proliferative diabetic retinopathy or diabetic macular edema	✓	✓
•	History of recurrent infectious or inflammatory ocular disease. Note: subjects with mild blepharitis will be allowed.	✓	✓

5.4 Microperimetry (MP) Criteria (At Selected Sites Only)

5.4.1 MP Inclusion Criteria

Microperimetry screening test criteria for eligibility:

1. Must be able to detect fixation target.
2. Total elapsed time to complete the 10-2 68-point exam is ≤ 30 minutes in duration.
3. Reliability Test ratio ≤ 20% (false positive rate).
4. Ability and willingness to undertake MP assessment as determined by Investigator.

5.4.2 MP Exclusion Criteria

1. Investigator determines that subject is unable to perform the test reliably.
   Note: disqualification from the microperimetry assessment does not exclude a subject from the trial participation if she/he qualifies as per the rest of the study entry criteria.

6 Study Treatment

6.1 Clinical Supplies

6.1.1 NGM621

NGM621 is an ~ 150 kDa protein expressed [redacted].

NGM621 drug product will be provided as a single use sterile solution for intravitreal injection. It is filled [redacted].

The targeted NGM621 concentration is [redacted] in formulation buffer containing [redacted]

6.2 Administration/ Handling/ Storage/ Accountability

6.2.1 Administration

6.2.1.1 NGM621

The injection procedure should be carried out under aseptic conditions, with hand washing, and the use of sterile gloves and a mask. Sterile paracentesis equipment should be available should it be required. Please refer to the Study Pharmacy Manual for additional detail related to administration.

6.2.1.2 Sham

Subjects randomized to the control arms will receive Sham injections Q4W or Q8W during the 12-month treatment period and will undergo the same assessments as the NGM621 treatment arm (see SOA: Table 4 and Table 5).

Sham injection is a procedure that mimics an intravitreal injection of NGM621, except that the blunt end of an empty syringe is pressed against an anesthetized eye instead of a needle attached to a NGM621-filled syringe (see Study Pharmacy Manual for details).

6.2.2 Storage and Stability

NGM621 vials are to be stored at 5°C ± 3°C upon receipt and should be kept in their packaging until use. Further instructions are included in the Study Pharmacy Manual. Vials are packaged in a vials/carton configuration for clinical administration.

6.2.3 Accountability

The PI is responsible for ensuring that a current record of inventory/drug accountability is maintained. Inventory records must be readily available for inspection by the study monitor and are open to inspection by regulatory authorities at any time.

Upon receipt of the investigational drug, the designated site personnel will visually inspect the shipment, verify the number and condition of study drug received, and confirm receipt of study drug.

At the completion of the study, all unused study drug supplies will be returned to the Sponsor (or designee) or disposed of by the clinic, per the Sponsor's (or designee's) written instructions.

6.3 Randomization

After written informed consent has been obtained, all subjects will receive a subject identification assigned through the Interactive Response Technology (IRT).

A subject must satisfy all eligibility criteria prior to randomization. As part of the screening process, the central reading center (masked to subject treatment assignment) will evaluate FAF, CFP, SD-OCT, and FA images to provide an objective, masked assessment of subject eligibility. In addition, treatment assignment/regimen will be masked to the specific site personnel, study subjects, sponsor study team, and sponsor Medical Monitor throughout the study period. After all subject eligibility requirements are confirmed, site personnel will contact the IRT on Day 1 visit for assignment of the study treatment (NGM621 or Sham). Subjects will be randomized in a 2:1:2:1 ratio to one of the study treatments arms (NGM621 Q4W, Sham Q4W, NGM621 Q8W, or Sham Q8W). The randomization will be stratified by subjects' baseline CNV status (Yes/No) in the fellow (non-study) eye.
The subjects will be randomized on the same day the study treatment is to be initiated (Day 1 visit).

6.3.1 Masking

This is a double-masked study. There must be a minimum of two investigators per site to fulfill the masking requirements of this study. Study visits must be scheduled when both investigators are present. At least one investigator will be designated as the evaluating physician who will be masked to subjects' treatment assignment and will evaluate all ocular assessments. At least one other investigator (and designated, unmasked assistant, as needed) will be designated as the treating (injecting) physician who will be unmasked to subjects' treatment assignment and will administer injections (NGM621 or Sham). The Principal Investigator must be masked to subjects' treatment assignment. All roles for each study staff

member should be clearly documented on the Site Delegation Log. The Delegation Log should be signed by the Principal Investigator.

Once the designated masked vs. unmasked roles are delineated and the site study staff have started to perform them, the roles cannot be switched or reversed at any time during the conduct of the study. In the event an alternate investigator needs to be substituted for an investigator, that alternate physician may assume only one role (i.e., treating physician or evaluating physician) for the duration of the study and must receive sponsor approval. In case a site is experiencing unexpected extreme situations, the sponsor's permission might be granted to switch an investigator/the study staff member from the masked role (evaluating physician) to the unmasked role (treating physician), but not the other way around.

Starting at the subject's Day 1 visit, the treating physician(s) performing the NGM621 or Sham injections and post-treatment finger counting, must continue their role as treating physician only. They cannot be involved in any other aspect of the study and must not divulge treatment assignment to anyone. Subjects, study site personnel (with the exception of the treating physician[s], assistant[s], and pharmacist if any), the designated evaluating physician(s), central reading center personnel, and the Sponsor and its agents (with the exception of drug accountability monitors) will be masked to treatment assignment.

The VA examiner (performing BCVA examinations and reading speed assessment) will be masked to subject treatment assignment and the treated study eye and will only perform BCVA, BCVA under low luminance conditions (LLVA), and reading speed assessments. The BCVA examiner will have no access to the VA scores of a subject's previous visits. The VA examiner is not allowed to perform any other tasks involving direct subject care.

Every effort must be made to limit the number of unmasked study personnel to ensure the integrity of this masked study. There must be no more than five unmasked personnel at an investigative site at one time. In special circumstances more than five unmasked personnel may be permitted after consultation with the medical monitor. Documented procedures will be put in place to avoid inadvertently unmasking study team members. Only the IRT provider responsible for verifying a subject's randomization and study treatment assignment, who are not otherwise involved in the study, will have access to the unmasking code. For the duration of the study, the subject treatment assignment will not be unmasked unless required for subject safety.

All study visit assessments, except those at screening, should be performed by masked site personnel only. Starting at Day 1 visit, the unmasked treating physician will only perform the study treatment and post-treatment vision testing (finger counting and, if applicable, hand movement and/or light perception). The injecting physician will also perform injection for CNV treatment as described in Section 7.3.15.

Study assessments include PK sample collection in all subjects (Section 7.3.6).
While PK samples must be collected from subjects assigned to the Sham arm to maintain the masking of treatment assignment, PK assay results for these subjects are generally not needed for the safe conduct or proper interpretation of this study. Sponsor personnel responsible for performing PK assays will be unmasked to subjects' treatment assignments to identify appropriate PK samples to be analyzed. Samples from subjects assigned to the Sham arm will not be analyzed except by request (i.e., to evaluate a possible error in dosing).

6.3.2 Removal of Study Masking (If Applicable)

Unmasking will be available to the PI in the event of a medical emergency or an AE that necessitated identification of the study drug for the welfare of that subject. Except in the case of a medical emergency, the PI and clinic staff will remain masked during the conduct of the study and until such time that all discrepancies in the clinical database are resolved (i.e., at the time of the database lock). The date and time when the PI removed the study masking for an individual subject will be documented, and a notification will be sent to the Sponsor.
The contracted CRO's pharmacovigilance team may also be required to break the mask for regulatory reporting purposes and if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected suspected adverse reactions that are considered by the investigator or Sponsor to be related to study drug.

6.4 Concomitant Medications

Any medication (including ocular) taken at least once within 28 days prior to Screening Visit and during the study period as well as the reason for use will be recorded in the source documents and the electronic case report forms (eCRFs); other than protocol-specified procedural medications (e.g., dilating drops or fluorescein dyes) and pre- and post-injection medications (e.g., proparacaine or antimicrobials [if applicable]) used by a subject within 7 days preceding Day 1 visit. Subjects should refrain from the use of any new prescription medications or products or change in the dose or frequency of existing therapies from Screening to Day 1 until EOS.

In addition, any invasive ocular procedure from the previous 5 years must be recorded in the source document (including start and stop dates).

The Medical Monitor should be informed of changes or addition of medications during this time period.

The following are prohibited from within 5 half-lives or 90 days, whichever is longer, prior to study entry through to the end of study:

- Investigational agents, other than NGM621, or devices for any indication

In addition, agents used for the treatment of any condition listed in the exclusionary enrollment criteria are prohibited from 28 days prior to Day 1 and through the end of study.

Note: This list of excluded medications/therapies is not an exhaustive list. Investigator judgement must be used to justify initiating any study medication during the study.

6.5 Permitted Therapies

Subjects required to use medications that are prohibited (see Section 6.4) will not be eligible for the study. Subjects who use other maintenance therapies should continue their use. Of note, the following are some common therapies that are permitted:

- Onset of ocular hypertension or glaucoma in the study eye during a subject's study participation should be treated as clinically indicated.
- Onset of cataract or posterior capsular opacification in either eye during the subject's study participation may be treated as clinically indicated. Dose-interruption criteria (see Section 6.7, Table 3) may apply with cataract surgery.
- Short-term use of topical corticosteroids after cataract surgery, YAG capsulotomy, or peripheral iridotomy.
- Oral corticosteroids at doses ≤ 10 mg/day prednisone or equivalent

6.6 Lifestyle Considerations/Restrictions

Female subjects of childbearing potential and male subjects with a female partner of childbearing potential must agree to either be abstinent or use consistent and adequate birth control from Screening to End of Study (EOS / Week 56). One of the following forms of contraception is required:

a) Condom
b) Hormone-containing contraceptive
c) Intrauterine device with a failure rate < 1% per year
d) Cervical cap or diaphragm with spermicidal agent
e) Tubal sterilization
f) Vasectomy in male partner

6.7 Discontinuation of Subjects from Study Participation

Subjects will be informed that they are free to withdraw from the study at any time and for any reason. The subject can also decide to discontinue study treatment but continue the remaining study assessments / visits (in this case the subject would be designated a treatment discontinuation rather than a study discontinuation). The PI may remove a subject from the study if, in the PI's opinion, it is not in the best interest of the subject to continue the study.

Subjects may be discontinued due to a change in compliance with an inclusion/exclusion criterion that is clinically relevant and affects subject safety, occurrence of AEs (Table 3), occurrence of pregnancy, or administration of non-permitted concomitant medication that might affect subject safety or study assessments/objectives. Notification of discontinuation will be made immediately to the Sponsor Medical Monitor or designee. In case of premature discontinuation of study participation, efforts will be made to perform all final EOT visit/assessments (see Table 4 and Table 5). The date the subject is withdrawn from the study and the reason for discontinuation will be recorded on the subject's eCRF. All withdrawn subjects will be followed until resolution of any AEs or until any unresolved AEs are judged by the PI to have stabilized.

Table 3. Dose -Interruption and Treatment Discontinuation Criteria

Event	Dose-Interruption Criteria
Intraocular inflammation	Interrupt study treatment if intraocular inflammation (iritis, iridocyclitis, uveitis, or vitritis) is ≥ 1+ in the study eye (see the grading scales of intraocular inflammation in Appendix 1. Subjects with ≥ 3+ intraocular inflammation will be discontinued from the study treatment.
VA loss	Interrupt study treatment if there is a treatment-related decrease in BCVA of ≥ 30 letters in the study eye compared with the last assessment of BCVA prior to the most recent treatment or from baseline BCVA at Study Day 1. Study treatment may be permitted subsequently as determined by the Sponsor and Investigator.
Elevated IOP	Interrupt study treatment if IOP in the study eye is ≥ 30 mm Hg. Treatment may be permitted when IOP has been lowered to < 30 mm Hg, either spontaneously or by treatment, as determined by the Investigator.
Vitreous hemorrhage	Interrupt study treatment in the event of a vitreous hemorrhage in the study eye. Study treatment may be permitted subsequently as determined by the Sponsor and Investigator.
Rhegmatogenous retinal break	Interrupt study treatment if a retinal break is present in the study eye. Study treatment may be resumed no earlier than 30 days after successful laser retinopexy as determined by the Investigator.
Rhegmatogenous retinal detachment or macular hole	Discontinue subjects from study treatment for the duration of the study if rhegmatogenous retinal detachment or Stage 3 or 4 macular holes is observed.
Active local or systemic infection	Interrupt study treatment if any of the following are present: infectious conjunctivitis, infectious keratitis, infectious scleritis, or endophthalmitis in either eye or if the subject is currently receiving treatment for an active *local or* systemic infection. Subjects with endophthalmitis in the study eye will be discontinued from the study treatment.
Cataract surgery in study eye	Interrupt study treatment after cataract surgery in study eye. Study treatment may be resumed no earlier than 30 days after an uncomplicated cataract surgery and no evidence of post-operational inflammation. For cataract surgery with complications, study treatment may be permitted as determined by Sponsor and Investigator.
Oral corticosteroids (prednisone >10 mg/day or equivalent	Interrupt study treatment. Study treatment may be resumed when oral corticosteroids dosing is prednisone ≤ 10 mg/day or equivalent.
IV corticosteroids	Interrupt study treatment. Study treatment may be resumed when the subject has finished IV corticosteroid course and oral corticosteroid dosing is prednisone ≤ 10 mg/day or equivalent.

BCVA = best corrected visual acuity; IOP = intraocular pressure; IV = intravenous; VA = visual acuity; YAG = yttrium aluminum garnet

If a subject misses more than 2 doses of study treatment within any 24-week treatment period, the Investigator and the Sponsor may consider discontinuing the subject from the study treatment.

7 Study Procedures

7.1 Schedule of Study Procedures

Tabular summaries of the assessments planned are presented in Table 4 for subjects in the Q4 weeks arm and Table 5 for subjects in the Q8 weeks arm. The dosing schedule for both arms (NGM621 and sham) is presented in Table 6.

Table 4. Q4 Week Arms Schedule of Assessments (NGM621 and Sham)

Study flowchart for Q4W Arms: Day 1, Week 1, Week 4 through Week 56

Activity/ Assessment	Screen	Baseline	Treatment														Follow Up
	Day -28 to -3	Day 1	Wk 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52 EOT [9]	Wk 56 EOS
Month				M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14
Visit Windows			±3	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
Informed Consent	X																
Inclusion/ Exclusion criteria	X																
Demographics	X															X	
Ocular/Medical History	X																
Physical Exam	X															X	
Body Weight	X															X	
Pregnancy Testing [1]	X	X														X	
Blood Sample (Hematology, chemistry) [2]	X															X	
Urine Sample (Urinalysis, Drug Screen)	X																
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X								X							X	X
FRI Index [3]		X							X							X	
NEI VFQ-25 [3]		X							X							X	
BCVA	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU
LLVA	OU								OU							OU	
Reading Speed		X							X							X	
Pre- and Post-dose IOP [4]	OU	OU	SE	SE	SE	OU	SE	SE	OU	SE	SE	OU	SE	SE	SE	OU	OU
Slit lamp Biomicroscopy	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU
Dilated Fundus Exam and Indirect Ophthalmoscopy	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU
SD-OCT [5]	OU						OU		OU		OU		OU			OU	OU

Activity/ Assessment	Screen	Baseline	Treatment														Follow Up
	Day -28 to -3	Day 1	Wk 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52 EOT [9]	Wk 56 EOS
Month				M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14
Visit Windows			±3	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
Fundus Autofluorescence (FAF) [6]	OU								OU							OU	
Fluorescein angiography (FA) [5]	OU																
Color Fundus Photography (CFP)	OU															OU	
Microperimetry at select sites (Study eye only) [7]	SE	SE							SE							SE	
Serum PK [8]		X	X	X			X		X				X		X	X	X
Serum ADA [8]		X		X			X		X				X		X	X	X
Serum NAb [8]		X		X			X		X				X		X	X	X
Serum – C3 and CH50		X	X	X					X							X	X
CCI [redacted]																	
Randomization		X															
CCI [redacted]																	
Dosing (Please see Table 6)																	

OU = both eyes; SE = study eye; X= Required.
[1] Females of childbearing potential only; Serum pregnancy test to be conducted at screening. Urine pregnancy test to be conducted on Day 1 and Week 52 visit. If pregnancy is suspected, a serum pregnancy test may be conducted.
[2] For the screening visit only, it is allowable to draw blood in the order of assessments as listed in the table OR the blood draw can occur right before the FA assessment to allow for a single needle stick.
[3] The patient-reported outcome (PRO) measures (NEI VFQ-25 and FRI Index) will be administered by the masked site staff (except for the VA examiner) prior to any other visit assessments being performed.
[4] Reference Section 7.3.12.1 and the pharmacy manual for details.
[5] A FA and SD-OCT should be performed if the development of CNV is suspected in study eye. The central reading center must confirm this finding before any intervention is initiated. See Section 7.3.15 for details.
[6] After randomization, if a patient misses a study visit when FAF images were scheduled to be taken, the images should be taken at the next scheduled visit.

[7] Microperimetry is optional and applies to select sites.
[8] PK, Anti-drug antibody and neutralizing antibody samples will be collected at Day 1 pre-dose, Week 1 post-dose (PK collection only), Weeks 4, 16, 24, 44, 48 pre-dose, and Weeks 52 and 56.
[9] For subjects who discontinue early from the study, the EOT visit assessments should be performed after a minimum of 28 days has elapsed from the last administered dose. See Section 6.7 for details.
[10] For subjects who consented to the optional sample collection.

Table 5. Q8 Week Arms Schedule of Assessments (NGM621 and Sham)

Study flowchart for Q8W Arms: Day 1, Week 1, Week 4 through Week 56

	Screen	Baseline	Treatment														Follow Up
Activity/Assessment	**Day -28 to -3**	**Day 1**	**Wk 1**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52 EOT [10]**	**Wk56 EOS**
Month				**M1**	**M2**		**M4**		**M6**		**M8**		**M10**		**M12**	**M13**	**M14**
Visit Windows			**±3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**
Informed Consent	X																
Inclusion/Exclusion criteria	X																
Demographics	X															X	
Ocular/Medical History	X																
Physical Exam	X															X	
Body Weight	X															X	
Pregnancy Testing [1]	X	X														X	
Blood Sample (Hematology, chemistry) [2]	X															X	
Urine Sample (Urinalysis, Drug Screen)	X																
Adverse Events [3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X								X							X	X
FRI Index [4]		X							X							X	
NEI VFQ-25 [4]		X							X							X	

Activity/Assessment	Screen	Baseline	Treatment													Wk 52 EOT [10]	Follow Up Wk56 EOS
	Day -28 to -3	Day 1	Wk 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48		
Month				M1	M2		M4		M6		M8		M10		M12	M13	M14
Visit Windows			±3	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
BCVA	OU	OU	OU	OU	OU		OU		OU		OU		OU		OU	OU	OU
LLVA	OU								OU							OU	
Reading Speed		X							X							X	
Pre- and Post-dose IOP [5]	OU	OU	SE		SE		SE		OU		SE		SE		SE	OU	OU
Slit lamp Biomicroscopy	OU	OU	OU	OU	OU		OU		OU		OU		OU		OU	OU	OU
Dilated Fundus Exam and Indirect Ophthalmoscopy	OU	OU	OU	OU	OU		OU		OU		OU		OU		OU	OU	OU
SD-OCT [6]	OU						OU		OU		OU		OU			OU	OU
Fundus Autofluorescence (FAF) [7]	OU								OU							OU	
Fluorescein angiography (FA) [6]	OU																
Color Fundus Photography (CFP)	OU															OU	
Microperimetry at select sites (Study eye only) [8]	SE	SE							SE							SE	
Serum PK [9]		X	X	X	X		X		X				X		X	X	X
Serum ADA [9]		X		X	X		X		X				X		X	X	X
Serum NAb [9]		X		X	X		X		X				X		X	X	X
Serum – C3 and CH50		X	X	X					X								X
CCI																	
Randomization		X															
CCI																	
Dosing (please see Table 5)																	

OU = both eyes; SE = study eye; X= Required

[1] Females of childbearing potential only; Serum pregnancy test to be conducted at screening. Urine pregnancy test to be conducted on Day 1 and Week 52 visit. If pregnancy is suspected, a serum pregnancy test may be conducted.
[2] For the screening visit only, it is allowable to draw blood in the order of assessments as listed in the table OR the blood draw can occur right before the FA assessment to allow for a single needle stick.
[3] Columns shaded gray indicate that adverse event reporting will be by telephone ( ) for non-visit months (Weeks 12, 20, 28, 36, and 44) for subjects in the Q8W arm only.
[4] The patient-reported outcome (PRO) measures (NEI VFQ-25 and FRI Index) will be administered by the masked site staff (except for the VA examiner) prior to any other visit assessments being performed.
[5] Reference Section 7.3.12.1 and the pharmacy manual for details.
[6] A FA and SD-OCT should be performed if the development of CNV is suspected in study eye. The central reading center must confirm this finding before any intervention is initiated. See Section 7.3.15 for details.
[7] After randomization, if a patient misses a study visit when FAF images were scheduled to be taken, the images should be taken at the next scheduled visit.
[8] Microperimetry is optional and applies to select sites.
[9] PK, anti-drug antibody and neutralizing antibody samples will be collected at Day 1 pre-dose, at Week 1 post-dose (PK collection only), Week 4 post-dose, Weeks 8, 16, 24, 40, 48 pre-dose, and on Weeks 52 and 56.
[10] For subjects who discontinue early from the study, the EOT visit assessments should be performed after a minimum of 28 days has elapsed from the last administered dose. See Section 6.7 for details.
[11] For subjects who consented to the optional sample collection.

Table 6. Dosing Treatment Arms (NGM621 and Sham)

	Screen	Baseline	Treatment														Follow Up
Treatment Arm	Day -28 to -3	Day 1	Wk 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52 EOT	Wk 56 EOS
NGM621 15 mg Q4W		X[1]		X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]		
Sham Q4W		X[1]		X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]		
NGM621 15 mg Q8W		X[1]			X[1]		X[1]		X[1]		X[1]		X[1]		X[1]		
Sham Q8W		X[1]			X[1]		X[1]		X[1]		X[1]		X[1]		X[1]		

[1] Refer to Section 7.3.12.1 and the pharmacy manual for details on treatment administration and pre- and post-dose IOP monitoring, and if needed, IOP management instructions.

7.2 Study Visit Procedures

7.2.1 Screening (Day –28 to Day –3) Visit

The following procedures will be performed at Screening:

- Obtain informed consent
- Inclusion/exclusion criteria assessment
- Demographics
- Ocular and medical history
- Physical Exam
- Measure body weight
- Serum pregnancy test for female subjects of child-bearing potential
- Hematology, Chemistry
- Urinalysis
- Urine drug screen
- Collect adverse events and concomitant medications
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)
- BCVA on both eyes
- LLVA on both eyes
- Intraocular pressure on both eyes
- Slit lamp biomicroscopy on both eyes
- Dilated fundus exam and indirect ophthalmoscopy on both eyes
- SD-OCT on both eyes
- Fundus autofluorescence on both eyes

- Fluorescein angiography on both eyes
- Color fundus photography on both eyes
- Microperimetry (at selected sites) on study eye
- Schedule Day 1 visit

7.2.2 Baseline (Day 1) Treatment Visit

The following procedures/assessments will be performed:

PRE-DOSE

- Urine pregnancy test for female subjects of child-bearing potential. If pregnancy is suspected, a serum pregnancy test may be conducted
- Adverse events and concomitant medications
- FRI Index
- NEI VFQ-25
- BCVA on both eyes
- Measure reading speed
- Intraocular pressure on both eyes (prior to dilating eyes)
- Slit lamp biomicroscopy on both eyes
- Dilated fundus exam and indirect ophthalmoscopy on both eyes
- Microperimetry (at selected sites) on study eye
- Serum sample for PK
- Serum samples for ADA and NAb
- Serum sample for C3 and CH50
- CCI [redacted]
- CCI [redacted]
- Randomize and dose all subjects (Q4W and Q8W), as randomized

POST-DOSE

- Level of vision (including finger counting, hand motion, and light perception) within 15 minutes post-dose on both eyes
- IOP post-dose on both eyes
- Schedule the next study visit

7.2.3 Week 1 (± 3 days) Visit

The following procedures/assessments will be performed:

- Adverse events and concomitant medications
- BCVA on both eyes
- IOP on study eye (prior to dilating eyes)
- Slit lamp biomicroscopy on both eyes
- Dilated fundus exam and indirect ophthalmoscopy on both eyes
- Serum sample for PK
- Serum sample for C3 and CH50.
- CCI [redacted]
- CCI [redacted]
- Schedule the next study visit

7.2.4 Week 4 (± 5 days) Treatment Visit

The following procedures/assessments will be performed:

PRE-DOSE

- Adverse events and concomitant medications
- BCVA on both eyes
- IOP on study eye (prior to dilating eyes)
- Slit lamp biomicroscopy on both eyes

- Dilated fundus exam and indirect ophthalmoscopy on both eyes
- Serum sample for PK
- Serum samples for ADA and NAb
- Serum sample for C3 and CH50
- CCI [redacted]
- CCI [redacted]
- Dose Q4W subjects ONLY, as randomized

POST-DOSE (Only Q4W arms)

- Level of vision (including finger counting, hand motion, and light perception) within 15 minutes post-dose on study eye
- IOP on study eye
- Schedule the next study visit

7.2.5 Week 8 (± 5 days) Treatment Visit

The following procedures/assessments will be performed:

PRE-DOSE

- Adverse events and concomitant medications
- BCVA on both eyes
- IOP on study eye (prior to dilating eyes)
- Slit lamp biomicroscopy on both eyes
- Dilated fundus exam and indirect ophthalmoscopy on both eyes
- Serum sample for PK (Q8W arms only)
- Serum samples for ADA and NAb (Q8W arms only)
- Dose all subjects (Q4W and Q8W), as randomized

POST-DOSE

- Level of vision (including finger counting, hand motion, and light perception) within 15 minutes post dose on study eye
- IOP post-dose on study eye
- Schedule the next study visit

7.2.6 Week 12 (± 5 days) Treatment Visit (Q4W Arms ONLY)

The following procedures/assessments will be performed:

PRE-DOSE

- Adverse events and concomitant medications
- BCVA on both eyes
- IOP on both eyes (prior to dilating eyes)
- Slit lamp biomicroscopy on both eyes
- Dilated fundus exam and indirect ophthalmoscopy on both eyes
- Dose Q4W subjects ONLY, as randomized

POST-DOSE

- Level of vision (including finger counting, hand motion, and light perception) within 15 minutes post dose on both eyes
- IOP post-dose on both eyes.
- Schedule the next study visit

7.2.6.1 Week 12 (± 5 days) Telephone Safety Visit (Q8W Arms ONLY)

- The sites will contact subjects in the Q8W treatment arm via a telephone call to record adverse events and concomitant medications.

7.2.7 Week 16 (± 5 days) Treatment Visit

The following procedures/assessments will be performed:

PRE-DOSE

- Adverse events and concomitant medications.
- BCVA on both eyes
- IOP on study eye (prior to dilating eyes)
- Slit lamp biomicroscopy on both eyes
- Dilated fundus exam and indirect ophthalmoscopy on both eyes
- SD-OCT on both eyes
- Serum sample for PK
- Serum samples for ADA and NAb
- Dose all subjects (Q4W and Q8W), as randomized.

POST-DOSE

- Level of vision (including finger counting, hand motion, and light perception) within 15 minutes post-dose on study eye
- IOP post dose on study eye
- Schedule the next study visit

7.2.8 Week 20 (± 5 days) Treatment Visit (Q4W Arms ONLY)

The following procedures/assessments will be performed:

PRE-DOSE

- Adverse events and concomitant medications
- BCVA on both eyes
- IOP on study eye (prior to dilating eyes)
- Slit lamp biomicroscopy on both eyes

- Dilated fundus exam and indirect ophthalmoscopy on both eyes
- Dose Q4W subjects ONLY, as randomized

POST-DOSE

- Level of vision (including finger counting, hand motion, and light perception) within 15 minutes post dose on study eye
- IOP post-dose on study eye
- Schedule the next study visit

7.2.8.1 Week 20 (± 5 days) Telephone Safety Visit (Q8W Arms ONLY)

- The sites will contact subjects in the Q8W treatment arm via a telephone call to record adverse events and concomitant medications.

7.2.9 Week 24 (± 5 days) Treatment Visit

The following procedures/assessments will be performed:

PRE-DOSE

- Adverse events and concomitant medications
- Vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)
- FRI Index
- NEI VFQ-25
- BCVA on both eyes
- LLVA on both eyes
- Reading speed
- IOP on both eyes (prior to dilating eyes)
- Slit lamp biomicroscopy on both eyes
- Dilated fundus exam and indirect ophthalmoscopy on both eyes
- SD-OCT on both eyes

- Fundus autofluorescence on both eyes
- Microperimetry (at selected sites) on study eye
- Serum sample for PK
- Serum samples for ADA and NAb
- Serum sample for C3 and CH50
- CCI [redacted]
- CCI [redacted]
- Dose all subjects (Q4W and Q8W), as randomized

POST-DOSE

- Level of vision (including finger counting, hand motion, and light perception) within 15 minutes post-dose on both eyes
- IOP post-dose on both eyes
- Schedule the next study visit

7.2.10 Week 28 (± 5 days) Treatment Visit (Q4W Arms ONLY)

The following procedures/assessments will be performed:

PRE-DOSE

- Adverse events and concomitant medications.
- BCVA on both eyes
- IOP on study eye (prior to dilating eyes)
- Slit lamp biomicroscopy on both eyes
- Dilated fundus exam and indirect ophthalmoscopy on both eyes
- Dose Q4W subjects ONLY, as randomized

POST DOSE

- Level of vision (including finger counting, hand motion, and light perception) within 15 minutes post dose on study eye
- IOP post-dose on study eye
- Schedule the next study visit

7.2.10.1 Week 28 (± 5 days) Telephone Safety Visit (Q8W Arms ONLY)

- The sites will contact subjects in the Q8W treatment arm via a telephone call to record adverse events and concomitant medications.

7.2.11 Week 32 (± 5 days) Treatment Visit

The following procedures/assessments will be performed:

PRE-DOSE

- Adverse events and concomitant medications
- BCVA on both eyes
- IOP on study eye (prior to dilating eyes)
- Slit lamp biomicroscopy on both eyes
- Dilated fundus exam and indirect ophthalmoscopy on both eyes
- SD-OCT on both eyes
- Dose all subjects (Q4W and Q8W), as randomized

POST-DOSE

- Level of vision (including finger counting, hand motion, and light perception) within 15 minutes post dose on study eye
- IOP post-dose on study eye
- Schedule the next study visit

7.2.12 Week 36 (± 5 days) Treatment Visit (Q4W Arms ONLY)

The following procedures/assessments will be performed:

PRE-DOSE

- Adverse events and concomitant medications
- BCVA on both eyes
- IOP on both eyes (prior to dilating eyes)
- Slit lamp biomicroscopy on both eyes
- Dilated fundus exam and indirect ophthalmoscopy on both eyes

POST-DOSE

- Level of vision (including finger counting, hand motion, and light perception) within 15 minutes post-dose on both eyes
- IOP post-dose on both eyes
- Schedule the next study visit

7.2.12.1 Week 36 (± 5 days) Telephone Safety Visit (Q8W Arms ONLY)

- The sites will contact subjects in the Q8W treatment arm via a telephone call to record adverse events and concomitant medications.

7.2.13 Week 40 (± 5 days) Treatment Visit

The following procedures/assessments will be performed:

PRE-DOSE

- Adverse events and concomitant medications
- BCVA on both eyes
- IOP on study eye (prior to dilating eyes)
- Slit lamp biomicroscopy on both eyes
- Dilated fundus exam and indirect ophthalmoscopy on both eyes
- SD-OCT on both eyes

- Serum sample for PK
- Serum samples for ADA and NAb
- Dose Q4W & Q8W subjects, as randomized

POST-DOSE

- Level of vision (including finger counting, hand motion, and light perception) within 15 minutes post dose on study eye
- IOP post dose on study eye
- Schedule the next study visit

7.2.14 Week 44 (± 5 days) Treatment Visit (Q4W Arms ONLY)

The following procedures/assessments will be performed:

PRE-DOSE

- Adverse events and concomitant medications
- BCVA on both eyes
- IOP on study eye (prior to dilating eyes)
- Slit lamp biomicroscopy on both eyes
- Dilated fundus exam and indirect ophthalmoscopy on both eyes
- Dose Q4W subjects ONLY, as randomized

POST-DOSE

- Level of vision (including finger counting, hand motion, and light perception) within 15 minutes post-dose on study eye
- IOP post-dose on study eye
- Schedule the next study visit

7.2.14.1 Week 44 (± 5 days) Telephone Safety Visit (Q8W Arms ONLY)

- The sites will contact subjects in the Q8W treatment arm via a telephone call to record adverse events and concomitant medications.

7.2.15 Week 48 (± 5 days) Treatment Visit

The following procedures/assessments will be performed at Week 48:

PRE-DOSE

- Adverse events and concomitant medications
- BCVA on both eyes
- IOP on study eye (prior to dilating eye)
- Slit lamp biomicroscopy on both eyes
- Dilated fundus exam and indirect ophthalmoscopy on both eyes
- Serum sample for PK
- Serum samples for ADA and NAb
- Dose Q4W & Q8W subjects, as randomized

POST-DOSE

- Level of vision (including finger counting, hand motion, and light perception) within 15 minutes post-dose on study eye
- IOP post-dose on study eye
- Schedule the next study visit

7.2.16 Week 52 (± 5 days) – End of Treatment (EOT) Visit (also Early Termination visit for any subjects that discontinue before week 52)

The following procedures/assessments will be performed:

- Demographics
- Physical exam
- Measure body weight
- Urine pregnancy test for female subjects of child-bearing potential. If pregnancy is suspected, a serum pregnancy test may be conducted.
- Hematology, Chemistry

- Adverse events and concomitant medications
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)
- FRI Index
- NEI VFQ-25
- BCVA on both eyes
- LLVA on both eyes
- Reading speed
- IOP on both eyes (prior to dilating eyes)
- Slit lamp biomicroscopy on both eyes
- Dilated fundus exam and indirect ophthalmoscopy on both eyes
- SD-OCT on both eyes
- Fundus autofluorescence on both eyes
- Color fundus photography on both eyes
- Microperimetry (at selected sites) on study eye
- Serum sample for PK
- Serum samples for ADA and NAb
- Serum sample for C3 and CH50
- CCI [redacted]
- CCI [redacted]

7.2.17 Week 56 (± 5 days) – Follow up and End of Study Visit

The following procedures/assessments will be performed:

- Adverse events and concomitant medications

- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)
- BCVA on both eyes
- IOP on both eyes (prior to dilating eyes)
- Slit lamp biomicroscopy on both eyes
- Dilated fundus exam and indirect ophthalmoscopy on both eyes
- SD-OCT on both eyes
- Serum sample for PK
- Serum samples for ADA and NAb
- If patient consented to the optional buccal swab and it was not collected at a prior visit, please collect the sample
- This visit marks the end of study participation for all subjects

7.3 Study Assessments and Evaluations

7.3.1 Demographic/ Ocular Characteristics

Demographic characteristics including sex, age, race, and ethnicity and ocular characteristics such as eye/iris color will be recorded (Table 4 and Table 5).

7.3.2 Ocular/Medical and Surgical History

The Investigator or designee will collect a complete ocular, medical, and surgical history (Table 4 and Table 5). Smoking history will be collected.

7.3.3 Body Weight

Body weight will be collected as determined by the Schedule of Study Procedures (Table 4 and Table 5).

7.3.4 Vital Signs

Vital signs assessments will include temperature (C°), respiratory rate (breaths per minute), systolic and diastolic blood pressure (mmHg) and pulse rate (bpm). Blood pressure and pulse rate will be measured after the subject has been resting quietly in a seated position for at least

5 minutes. Any clinically significant abnormal vital sign assessment requires at least one repeat measurement.

Vital signs abnormalities that (1) are considered clinically significant initially and on confirmation, (2) require a subject to be discontinued from the study, or (3) require a subject to receive treatment will be recorded as AEs.

7.3.5 Physical Examination

A focused physical examination of specific body system(s) relating to any presenting problem or current concern(s) of the subject will be conducted. This may involve one or more body system. An eye exam including EOM movements will be performed, and abnormal findings will be carefully documented in the subject's eCRF. An abnormal physical examination finding that is considered clinically significant and requires the subject to be discontinued from the study or requires intervention will be recorded as an AE.

7.3.6 Clinical Laboratory Examinations

At the scheduled visit, specimens should be collected prior to study eye treatment and FAF assessments (if applicable). The specimens will be forwarded to the central laboratory. The central laboratory will either perform the analysis or forward samples to Sponsor or its designee for analysis and/or storage.

The Laboratory Manual will contain the necessary instructions for obtaining, processing, storing and shipping of all samples. Clinical laboratory kits will be provided to sites by the central laboratory.

The following assessments will be performed as indicated:

- Hematology: hemoglobin, hematocrit, quantitative platelet count, red blood cell counts, white blood cell counts, and differentials, including neutrophils, bands, lymphocytes, basophils, eosinophils, and monocytes (absolute)

- Chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, total and direct bilirubin, total protein, albumin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, and uric acid

- Urinalysis: pH, specific gravity, glucose, ketones, bilirubin, protein, urobilinogen and microscopic examination

- Initial serum pregnancy test (β-human chorionic gonadotropin) for women of childbearing potential, including those who have had tubal ligation. If positive, study treatment will not be administered.

- Urine pregnancy test prior to each study treatment for women of childbearing potential, including those who have had tubal ligation. If positive, perform the serum pregnancy test. If the serum pregnancy test is positive, do not administer the study treatment.
- Urine drug screen assessment
- Complement pathway assessment assay (C3 and CH50): In all subjects serum samples will be collected as outlined in Table 4 and Table 5.
- Systemic PK, ADA, and NAb Evaluation: Serum samples for PK, ADA, and NAb will be collected as outlined in Table 4 and Table 5. Processing, storage, and shipping instructions for these PK blood samples will be presented in the study Lab Manual.
- CCI [redacted]
- If the subject gave consent for any remaining blood (including plasma and serum) samples to be retained for optional research, then the samples may be stored for up to 15 years after the date of final closure of the associated clinical database.

7.3.7 BCVA/LLVA

Best corrected visual acuity will be measured by trained and certified personnel at the study sites. The visual acuity (VA) examiner must be masked to each subject's study (treated) eye and treatment arm (study drug vs. Sham) assignment. VA will be measured at the intervals specified in Table 4 and Table 5.

The name and certification number of the vision examiner should be documented in the subject's visual acuity (VA) worksheet (provided by the Sponsor or designee) at each visit. Retroilluminated ETDRS charts are used in this trial. Refraction should be conducted prior to visual acuity testing to obtain best-corrected vision. Best-corrected visual acuity at a starting distance of 4 meters is measured at all office-based study visits using standard charts, lighting, and procedures. The low luminance visual acuity (LLVA) has the same requirements as the best corrected visual acuity; however, the low luminance visual acuity will be measured by placing a 2.0-log-unit neutral density filter over the best correction for that eye and having the participant read the normally illuminated Early Treatment Diabetic Retinopathy Study chart.

A description of the VA assessment is detailed in the Study Procedure Manual or equivalent.

7.3.8 Reading Speed

7.3.8.1 The Minnesota Low-Vision Reading Test (MNRead)

The Minnesota Low-Vision Reading Test (MNRead) acuity cards are continuous-text reading-acuity cards suitable for measuring the reading acuity and reading speed of normal and low-vision subjects. The Subjects' average reading speed, critical print size, and reading acuity will be calculated using the data transcribed from the scoring sheet to the eCRF and will not be calculated by the interviewers. For additional details see the Study Procedure Manual or equivalent.

7.3.8.2 Radner Reading Cards

The Radner Reading Cards consist of "sentence optotypes," which are optimized reading test items, standardized by construction and statistical selection. The Radner Reading Cards are suitable for measuring reading speed, reading visual acuity, and critical print size.
The Radner Reading Cards are in the form of a letter-sized booklet with the reading cards and includes clear instructions and evaluation sheets. Eight sentences are printed per page. Each sentence of 14 words is printed on three lines and print sizes vary from 6.3 M to 0.25 M (20/400 to 20/16 at 32 cm). For additional details see the Study Procedure Manual or equivalent.

7.3.9 FRI Index

The FRI Index is a 7-item, interviewer-administered assessment of functional reading independence (see the Study Procedure Manual or equivalent). It has one total index score. The index score is an ordinal scale with higher levels representing higher functional reading independence. The FRI Index has a specified recall period of 7 days. For additional details see the Study Procedure Manual or equivalent.

7.3.10 NEI VFQ-25

The NEI VFQ-25 is a 25-item, interviewer-administered assessment of visual functioning. Near and distance domains will also be included (three additional items for each domain). It is scored on a scale of 0−100, with higher scores indicating better visual function. It has a composite score and 12 domains (general health, general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, and peripheral vision). It does not have a specified recall period. For additional details see the Study Procedure Manual or equivalent.

7.3.11 Slit Lamp Biomicroscopy

Slit lamp biomicroscopy will be performed as determined by the Schedule of Study Procedures (Table 4 and Table 5).

Grading scales based on the NEI/SUN criteria for the assessment of Anterior Chamber Flare or Cell (Jabs 2005) and Vitreous Cells and Haze (Nussenblatt 1985) are provided in Appendix 1.

Slit-lamp exam must be performed before the instillation of any dilating or anesthetic eye drops or fluorescein agent. Subject will remain seated for this exam.

7.3.12 Intraocular Pressure

Goldmann tonometry or Tono-pen tonometer is required at routine study visits for pre- and post-dose intraocular pressure assessments. The method of IOP measurement used for a patient must remain consistent throughout the study. If pathological measurements are obtained with Tono-pen, contact-tonometry should be performed.

7.3.12.1 Post Injection Assessment

A measurement of intraocular pressure of either the study eye or both eyes (depending on the visit; refer to Table 4 and Table 5) will be obtained approximately 15 minutes after any IVT injection by qualified unmasked site staff. If there are no safety concerns, the subject will be permitted to leave the clinic. The IOP values recorded in mmHg will be entered into the eCRF. If the IOP post-dose is ≥ 30 mmHg, the subject should remain in clinic and be measured again approximately 30 minutes later (45–60 minutes post-injection). Pressure lowering drops are permitted at Investigator discretion. If there are no safety concerns at that time, and the IOP is < 30 mmHg, the subject will be permitted to leave the clinic. The last post-injection IOP value will be recorded on the appropriate eCRF.

In the case of an acute IOP spike (≥ 30 mmHg from pre-injection IOP as measured at ≥ 60 minutes post-injection), which causes pain and loss of vision, a paracentesis may be performed in the anterior chamber, to release some aqueous humor and relieve the pressure. The final pre-intervention IOP recording as well as the post-intervention IOP recorded will be entered into the applicable eCRF page. If applicable, an Adverse Event eCRF page will be completed.

7.3.13 Dilated Fundus Exam and Indirect Ophthalmoscopy

Ophthalmoscopy will be performed as identified in the Schedule of Study Procedures (Table 4 and Table 5).

After the pupil is dilated, the optic nerve and macular are evaluated at the slit lamp with a 90/78/60 diopter (or similar) lens. This is followed by Indirect Ophthalmoscopy (IO) which examines for vitreous haze (the degree of inflammation) and the peripheral retina, looking for retinal tears after injection among other things. Both the slit lamp and IO are done together to evaluate the posterior segment.

7.3.14 Ocular Imaging

Central reading center will be used to perform an independent analysis of all images. The central reading center will provide sites with the Central Reading Center manual and training materials for specified study ocular images. Before any study images are obtained, site personnel, test images, and systems and software (where applicable) will be verified/validated by the reading center as specified in the Central Reading Center manual. All ocular images results will be obtained by trained site personnel at the study sites and forwarded to the central reading center for independent analysis and/or storage. Note: after randomization, if a subject misses a study visit during which ocular images were scheduled to be taken, the images should be obtained at the next scheduled visit (Table 4 and Table 5)

Ocular images obtained for the purpose of the study should include the following:

- Spectral domain Optical Coherence Tomography (SD-OCT)
- Fundus autofluorescence (FAF)
- Color Fundus Photography (CFP)
- Fluorescein angiography (FA)

Additional details on obtaining these images are included in the Central Reading Center Manual.

7.3.14.1 SD-OCT

Spectral Domain Optical Coherence Tomography (SD-OCT) will be collected as determined by the Schedule of Study Procedures (Table 4 and Table 5). SD-OCT will be performed at the study sites by trained personnel who are certified by the central reading center. SD-OCT imaging will be performed for each subject at the intervals specified in Table 4 and Table 5. Once images are collected, they will be forwarded to the central reading center.

7.3.14.2 Fundus Autofluorescence

Fundus Autofluorescence (FAF) will be performed at the study sites by trained personnel who are certified by the central reading center. FAF imaging will be performed for each subject at the intervals specified in Table 4 and Table 5. Once images are collected, they will be forwarded to the central reading center.

7.3.14.3 Color Fundus Photography (CFP)

Color Fundus Photography (CFP) will be taken by trained personnel at the study sites. Fundus photography will be performed at the intervals specified in Table 4 and Table 5. Once images are collected, they will be forwarded to the central reading center.

7.3.14.4 Fluorescein Angiography (FA)

Fluorescein angiography will be performed at the study sites by trained personnel who are certified by the central reading center. The fluorescein angiograms (FAs) will be obtained at the intervals specified in Table 4 and Table 5. Once images are collected, they will be forwarded to the central reading center.

7.3.14.5 Microperimetry

Mesopic microperimetry of study eye only will be performed at select study sites by trained personnel who are certified by the central reading center. Microperimetry will be performed on subjects who meet eligibility criteria as defined in Section 5.

The microperimetry results of the study eye will be obtained at protocol-specified visits, as specified in Table 4 and Table 5, and will be forwarded to the central reading center for additional review.

7.3.15 Management of Choroidal Neovascularization (CNV)

While subjects with active CNV in their study eyes are excluded from this study, it is possible that CNV develops during the duration of the study.

Diagnosis: Subjects suspected of clinical CNV development in the study eye must have the diagnosis confirmed with SD-OCT and FA. CNV confirmation by the Central Reading Center, using both imaging modalities, is required prior to initiation of anti-VEGF treatment. On the study visit where CNV is suspected by the evaluating physician, and the additional imaging is taken and submitted for Central Reading Center review, it is allowable to proceed with the study dosing per the assessment schedule while awaiting Central Reading Center feedback on CNV diagnosis. Once the diagnosis is confirmed the patient can be administered aflibercept (EYLEA®). This may require a separate visit (unscheduled visit). If there is a patient safety concern please reach out to the medical monitor to discuss management.

7.3.15.1 Management of Choroidal Neovascularization (CNV)-Study Eye

Treatment (Study Eye): In this protocol, only aflibercept (EYLEA®) is allowed. Follow routine clinical practice in administering aflibercept per FDA label. Treatment frequency with anti-VEGF should be based on standard of care regimens to maximize long-term visual outcomes and minimize recurrence and subject burden.

Study Drug (Study Eye): In subjects who developed CNV in their study eye and have a confirmed diagnosis from the Central Reading center, study drug will continue but it will be administered after anti-VEGF treatment, once the IOP has returned to a normal range (< 30 mmHg), approximately 15–30 minutes after the anti-VEGF injection. At the

physician's discretion, maneuvers such as mild ocular digital massage may be applied to the globe prior to the injection to reduce the risk of complications secondary to increased IOP.

A measurement of intraocular pressure will be obtained approximately 15 minutes after the second IVT injection by qualified unmasked site staff. If there are no safety concerns, the subject will be permitted to leave the clinic. The IOP values recorded in mmHg will be entered into the eCRF. If the IOP post dose is ≥ 30 mmHg, the subject should remain in clinic and be measured again approximately 30 minutes later (45–60 minutes postinjection). Pressure lowering drops are permitted at Investigator discretion. If there are no safety concerns at that time, and the IOP is < 30 mmHg, the subject will be permitted to leave the clinic. The last postinjection IOP value will be recorded on the appropriate eCRF.

In the case of an acute IOP spike (≥ 30 mmHg from preinjection IOP as measured at ≥ 60 minutes post the second injection), which causes pain and loss of vision, a paracentesis may be performed in the anterior chamber, to release some aqueous humor and relieve the pressure. The final preintervention IOP recording as well as the postintervention IOP recorded will be entered into the applicable eCRF page. If applicable, an Adverse Event eCRF page will be completed.

Study Subject (Study Eye): Subjects receiving CNV treatment will continue in the study until end of the study (Week 56). If subjects opt to discontinue study drug, they should still continue with study visits and assessments through Week 56.

7.3.15.2 Management of Choroidal Neovascularization (CNV)-Non-Study Eye

Treatment (Non-Study Eye): In subjects with CNV in the non-study (fellow) eye, follow routine clinical standard of care in diagnosis and treatment. If non-study eye treatment will occur on the same day as a study dosing visit, the study eye should be dosed first. There are no other specific treatment stipulations for non-study eye.

Study Drug (Non-Study Eye): In subjects with CNV in the non-study (fellow) eye, study drug will not be stopped.

Study Subject (Non-Study Eye): Subject will continue in the study until end of the study.

7.3.16 Clinical Genotyping Sample

An optional one-time buccal swab will be collected for genetic marker analysis at any time during the study post-randomization (Day 1 to EOS). Collection will only occur if the subject has consented to the optional procedure on the consent form and there are no laws or study center policies in place that prohibit the collection of samples for genetic marker analysis. The genetic marker sample will be used to evaluate the relationships between genetic polymorphisms associated with AMD, baseline disease characteristics, and response to

administration of NGM621. If a subject does not want to participate in this optional sample collection, this does not preclude their participation in the trial.

7.4 Safety and Other Assessments

7.4.1 Adverse Events

7.4.1.1 Definition of Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigational subject who has been administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. A treatment-emergent adverse event (TEAE) is an AE that is reported after a dose of study drug.

AEs are all:

- unfavorable changes in general condition.
- subjective or objective signs/symptoms.
- concomitant diseases or accidents.
- clinically relevant adverse changes in laboratory parameters observed in a participant in the course of a clinical study.

AEs comprise all disturbances of general health status, subjective and objective disease symptoms (including laboratory abnormalities), and accidents observed in the context of a clinical trial, irrespective of a possible causal relationship with the administration of the trial substance. Events occurring in the framework of a clinical trial during drug-free, and post-treatment periods, or under placebo, are also to be designated as AEs.

All AEs, whether volunteered, elicited, or noted on physical examination, will be recorded throughout the study (i.e., from screening until end of study [EOS]).

Subjects will be queried for resolution of ongoing AEs or until any unresolved AEs are judged by the PI to have stabilized or if lost to follow up. Resolution of all AEs will be promptly documented by the clinic in the subject's eCRF.

Any pregnancy diagnosed during the study must be reported immediately to the Investigator and Sponsor, including pregnancy in female partners of male subjects. The pregnancy will be followed to term and/or outcome and this outcome must be reported to the Sponsor. Pregnancy, in and of itself, is not regarded as an AE or serious adverse event (SAE) unless the birth results in a congenital anomaly/birth defect or there is suspicion that the study treatment may have interfered with the effectiveness of a contraceptive medication or method.

The PI will rate the severity of systemic AEs and ocular AEs using different scales. The PI will rate the severity of systemic AEs using the CTCAE v5 to grade the severity. Each CTCAE v5 term is a Medical Dictionary for Regulatory Activities (MedDRA) Lowest Level Term (LLT). The CTCAE displays Grades 1–5 with unique clinical descriptions of severity for each AE. Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection. Grade 5 (Death) is not appropriate for some AEs and, therefore, is not an option.

The PI will rate the severity of ocular AEs using the definitions below. For each episode, the highest severity grade attained should be reported.

MILD = Does not interfere with subject's usual function (awareness of symptoms or signs, but easily tolerated [acceptable]).

MODERATE = Interferes to some extent with subject's usual function (enough discomfort to interfere with usual activity [disturbing]).

SEVERE = Interferes significantly with subject's usual function (incapacity to work or to do usual activities [unacceptable])

7.4.1.2 Definition of Serious Adverse Events and SAE Reporting

An SAE is any untoward medical occurrence at any dose that results in any of the following outcomes:

- Death
- A life-threatening event (i.e., puts the subject, in the view of the PI, at immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Important medical event that may require medical or surgical intervention to prevent one of the above outcomes

An unexpected adverse drug event is any adverse drug event the specificity or severity of which is not consistent with the current IB or, if an IB is not required or available, the general investigational plan or elsewhere in the current application.

An AE is associated with the use of the drug if a reasonable possibility exists that the event may have been caused by the drug.

SAEs that are unexpected and related to NGM621 are reportable to Regulatory Authorities. All SAEs will be reported by the PI to the Sponsor and will be reported to the responsible Ethics Committee (EC) in accordance with local requirements.

The Sponsor's assigned Safety Representative will be notified in writing (e.g., email or facsimile) within 24 hours of when an SAE is first recognized or reported. The Safety Representative will subsequently notify the Sponsor and the Sponsor's assigned Medical Monitor or designee of all reported SAEs.

7.4.1.3 Classification of Severity of Adverse Event

The severity of AEs will be categorized as shown below.

Categorization of Severity of Adverse Events

Mild	The event is minor and does not cause significant discomfort to subject or change in activities of daily living (ADL); participant is aware of symptoms, but symptoms are easily tolerated.
Moderate	The event is an inconvenience or concern to the subject and causes interference with ADL, but the participant is able to continue with ADL.
Severe	The event significantly interferes with ADL and the subject is incapacitated and/or unable to continue with ADL.
Potentially life threatening	An event/reaction in which the subject was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe.

7.4.1.4 Assessment of Causality of Adverse Events

The masked, evaluating investigators should use their knowledge of the subject, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an AE is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see Table 7):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study

- Presence of risk factors in the subject or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 7. Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?
YES *There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug and, if applicable, reappears upon re-challenge.* NO *An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).*

7.4.1.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording AEs on the Adverse Event eCRF. Avoid colloquialisms and abbreviations. Only one AE term should be recorded in the event field on the Adverse Event eCRF. For the purposes of reporting events of infection and inflammation, the following terms and definitions should be used:

- Iritis: the presence of inflammatory cells in the anterior chamber. Note: The presence of aqueous flare alone will not constitute iritis but should be documented as an anterior chamber flare for AE reporting purposes.
- Iridocyclitis: the presence of inflammatory cells in both the aqueous and vitreous
- Vitritis: the presence of active inflammation in the vitreous, demonstrated by the presence of inflammatory cells (trace or greater)

- Active inflammation in the vitreous should be clinically differentiated from cellular debris from prior episodes of inflammation, hemorrhage, or other causes.
- Endophthalmitis: diffuse intraocular inflammation predominantly involving the vitreous cavity but also involving the anterior chamber, implying a suspected underlying infectious cause. A culture is required prior to initiating antibiotic treatment for presumed endophthalmitis. Results of bacterial or fungal cultures, treatment given, and final ophthalmologic outcome should also be provided in the details section of the event eCRF.

Note: Trace benign, aqueous pigmented cells visible on slit-lamp examination that are caused by dilation and are not RBCs or WBCs or the result of any ocular disorder should not be recorded as an AE.

7.4.1.6 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

7.4.1.7 Adverse Events That Are Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.

- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All AEs should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

7.4.1.8 Sight Threatening Event

For this study medically important events comprise the following sight threatening events, which are considered to be of special interest and by default are to be reported as SAEs:

- Adverse Events that caused a decrease in visual acuity of > 30 ETDRS letters or > +0.6 LogMAR lasting > 1 hour, compared with the last assessment of visual acuity at the last visit or from baseline BCVA on Study Day 1.

- Adverse Events that cause a decrease in visual acuity to the level of Light Perception or worse lasting >1 hour.

- Adverse Events that require surgical intervention (e.g., conventional surgery, vitreous tap or biopsy with intravitreal injection of anti-infectives, or laser or retinal cryopexy with gas) to prevent permanent loss of sight.

- Adverse Events associated with severe intraocular inflammation (i.e., endophthalmitis, 4+ anterior chamber cell/flare or 4+ vitritis).

- Adverse Events that, in the opinion of the Investigator, may require medical intervention to prevent permanent loss of sight.

8 Statistical Considerations

A detailed statistical analysis plan (SAP) will be provided and finalized prior to the study database lock or unmasking. No discrepancies are expected between the SAP and the protocol. However, if there are discrepancies between this section of the protocol and the final SAP, the SAP will override the protocol.

In general, descriptive statistics including the number of non-missing observations (n), arithmetic mean (mean), standard deviation (SD), median, minimum (min), and maximum (max) will be presented by treatment group for continuous endpoints. Frequency and percentage distribution will be presented by treatment group for categorical endpoints.

8.1 Analysis Sets

Subjects will be analyzed using the following analysis sets:

- Modified Intent-To-Treat (mITT) Analysis Set: All randomized and treated (with at least one dose of study drug) subjects. This analysis set will be used for all efficacy analyses and subjects will be analyzed based on the treatment group into which they are randomized.
- Per Protocol (PP) Analysis Set: a subset of subjects in the mITT Analysis Set who have no protocol deviations that affect the GA lesion assessments (by FAF). This analysis set will be used for sensitivity analyses to support the mITT analyses.
- Safety Analysis Set: All treated subjects. This analysis set will be used for all safety analyses and subjects will be analyzed based on the actual treatment they receive.
- Pharmacokinetic (PK) Analysis Set: a subset of subjects in the Safety Analysis Set who have quantifiable PK measurements post first dose. This analysis set will be used for all PK analyses and subjects will be analyzed based on the actual treatment they receive.

8.2 Demographics and Other Baseline Characteristics

Demographics (e.g., age, sex, race, etc.) and other baseline characteristics (body weight, iris color, etc.) will be summarized with descriptive statistics by treatment group for each analysis set.

8.3 Efficacy Analyses

All efficacy analyses will be performed based on data collected for study eye whenever applicable. All efficacy analyses will be performed using the mITT Analysis Set. The PP Analysis Set will be used for sensitivity analyses to support the primary and secondary efficacy analyses (the mITT analyses).

8.3.1 Primary Efficacy Analyses

8.3.1.1 Primary Estimand

The estimand for the primary interest of this study is defined as follows:

1. Treatment: NGM621 Q4W, NGM621 Q8W, and pooled Sham (Sham injections Q4W or Q8W).
2. Population: subjects with geographic atrophy secondary to age-related macular degeneration as defined by the inclusion-exclusion criteria of the study.
3. Endpoint: rate of change in GA lesion area as measured by FAF over the 52 weeks of treatment.
4. Inter-current events and their corresponding strategies:

Intercurrent Events	Estimand Strategies
treatment or study discontinuation	Hypothetical "as own treatment group" strategy: Clinical course is the same as other subjects in the same treatment group, who had not discontinued study treatment.
treatment non-compliance	Treatment Policy strategy: All observed values of the variable are used, regardless of whether or not the subject had experienced the intercurrent event.
dose interruption	Treatment Policy strategy
initiation or adjustment of concomitant medication	Treatment Policy strategy
any other major protocol deviations	Treatment Policy strategy
intermediate events leading to intermediate missing for the FAF assessments	Hypothetical "as own treatment group" strategy

5. Population-level summary: the treatment group difference between each NGM621 group and the pooled Sham group in the mean change from baseline to Week 52 in GA lesion area as measured by FAF.

8.3.1.2 Main Estimation

The GA lesion area (at baseline, Week 24, and Week 52) will be analyzed using a random coefficients model. The model includes terms for time (continuous variable assuming linearity) and treatment-by-time interaction. The intercept and slope of time are assumed to

be random effects with a bivariate normal distribution and an unstructured (UN) covariance matrix while the treatment-by-time interaction is assumed to be a fixed effect. CCI [redacted] Within the framework of this model, a point estimate of the treatment group difference in the regression slope between each NGM621 group and the pooled Sham group will be provided.
The corresponding two-sided 95% confidence interval and p-value for the point estimate will also be presented.

A hierarchical testing procedure will be used to control the family-wise type-I error rate associated with the tests of the two NGM621 groups (NGM621 Q4W vs pooled Sham and NGM621 Q8W vs pooled Sham). Specifically, the comparison between NGM621 Q4W and pooled Sham will be performed first. If this test is statistically significant at the 5% level, then the comparison between NGM621 Q8W and pooled Sham will be performed. If the first test is not statistically significant at the 5% level, then the comparison between NGM621 Q8W and pooled Sham will be considered exploratory.

8.3.1.3 Sensitivity Analyses

Sensitivity analyses will be performed to assess the robustness of the main estimator of the primary estimand. These sensitivity analyses will be performed with missing data imputed by the multiple imputation approach using the Markov Chain Monte Carlo (MCMC) method, a placebo-based pattern mixture model, and a tipping point method, respectively. The details of these analyses will be provided in the SAP.

CCI [redacted] The within-subject errors are assumed to be independent and identically distributed normal random variables, and are assumed to be independent of the random intercept. The details of this analysis will be provided in the SAP.

8.3.2 Secondary Efficacy Analyses

Secondary efficacy endpoints include change from baseline at Week 52 in GA lesion area, the square root of GA lesion area, BCVA score, LLVA letter score, LLD in EDTRS letters at a starting distance of 4 meters, binocular reading speed (by MNRead or Radner reading charts), binocular critical print size (by MNRead or Radner reading charts), FRI composite score, and NEI VFQ-25, as well as change and percent change of CH50 from baseline at each visit.

The change from baseline will be analyzed using a linear mixed-effects model. The model includes fixed effects for treatment, visit, treatment-by-visit interaction, and the baseline outcome value as a covariate. The covariance structure for this model will be assumed to be unstructured. If the model does not converge under this assumption, then a compound symmetry covariance structure will be used. Within the framework of this model, a point estimate of the treatment group difference at Week 52 between each NGM621 group and the pooled Sham group will be provided. The corresponding two-sided 95% confidence interval and p-value for the point estimate will also be presented.

8.4 Safety Analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Ocular and systemic treatment emergent adverse events (TEAEs) will be summarized by primary system organ class and preferred term. Actual values and change from baseline values for vital signs, clinical laboratory (hematology and chemistry) tests and other continuous variables (both ocular and non-ocular) will be summarized with descriptive statistics. Concomitant medications, physical examinations, and other categorical (safety) variables (both ocular and non-ocular) will be summarized with frequency and percentage distribution. All safety analyses will be performed using the Safety Analysis Set.

8.5 Pharmacokinetics Analyses

Individual and mean serum NGM621 concentration–time data will be tabulated and plotted by cohort/dose level.

CCI [redacted]

Additional PK analyses and/or summary statistics will be conducted as appropriate. All PK analyses will be performed using the PK Analysis Set.

8.6 Sample Size Determination

Subjects will be randomized in a 2:1:2:1 ratio to receive treatment with NGM621 Q4W, Sham Q4W, NGM621 Q8W, or Sham Q8W. Subjects from the two Sham groups will be pooled in the data analysis.

A sample size of 106 subjects per treatment group (i.e., 318 subjects in total) is expected to provide approximately 90% (NGM621 Q4W vs pooled Sham) and 85% (NGM621 Q8W vs pooled Sham) power to detect a statistically significant treatment group difference in the rate of change in GA lesion area over the 52 weeks of treatment. The power is estimated based on simulations assuming a mean GA lesion area of 8 mm^2 at baseline for all subjects, a common standard deviation of 4 mm^2 for GA lesion area, a linear slope of 2 mm^2 per year for the

pooled Sham group, 1.4 mm^2 per year for NGM 621 Q4W and 1.45 mm^2 per year for NGM 621 Q8W, a within-subject correlation of 0.95, a statistical significance level of 5% (two-sided), and a 10% of subject dropout rate. These assumptions are based on published data

CCI [redacted]

CCI [redacted]

9 Supporting Documentation and Operational Considerations

9.1 Regulatory, Ethical, and Study Oversight Considerations

9.1.1 Informed Consent Process

This study will be conducted in compliance with International Conference on Harmonisation (ICH) E6 Good Clinical Practice: Consolidated Guidance pertaining to informed consent. At the first visit, prior to initiation of any study-related procedures, subjects must give their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits.
The informed consent document must be signed and dated by the subject prior to study participation. A copy of the informed consent document must be provided to the subject. Signed consent forms must remain in the subject's study file and be available for verification by Sponsor or its representative at any time.

9.1.2 Ethics Committee

This protocol, the informed consent document, and all relevant supporting data must be submitted to the IRB/EC for approval. IRB/EC approval of the protocol, informed consent document, and any advertisement used to recruit study subjects must be obtained before the study may be initiated.

The PI is responsible for keeping the IRB/EC advised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, at least once a year. The PI is also responsible for notifying the IRB/EC of any reportable adverse events (AEs) that occur during the study.

9.1.3 Protocol Adherence

The Investigator must adhere to the protocol as detailed in this document and agree that the Sponsor must approve any changes to the protocol prior to seeking approval from the IRB/EC. There will be no alterations in the protocol without agreement between the Sponsor and the Investigator. There will be no alterations in the protocol affecting subject safety without the express written approval of the Sponsor, Investigator, and the IRB/EC.

9.1.4 Confidentiality and Privacy

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. The Investigator agrees not to disclose such information in any way without prior written permission from the Sponsor.

Any publication of the results, either in part or in total (articles in journals or newspapers, oral presentations, abstracts, etc.) by the Investigator or their representative(s), shall require prior notification and review, within a reasonable time frame, by the Sponsor, and cannot be made in violation of the Sponsor's confidentiality restrictions or to the detriment of the Sponsor's intellectual property rights.

9.1.5 Clinical Monitoring

The Sponsor or designee (e.g., Clinical Research Associate (CRA)) will be responsible for monitoring this clinical trial. The CRA will monitor the study conduct, proper eCRF and source documentation completion and retention, and accurate study drug accountability. To this end, the CRA will visit the study site at suitable intervals and be in frequent contact through verbal and written communication. The Investigator will grant access to all documents (related to the study and the individual participants) at any time these are requested. In turn, the CRA will adhere to all requirements for participant confidentiality as outlined in the informed consent form (ICF). The Investigator and Investigator's staff will be expected to cooperate with the CRA, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information.

9.1.6 Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion. An individualized quality management plan may be developed to describe a site's quality management.

9.1.7 Records

The results from Screening and data collected during the study will be recorded in the subject's eCRF. To maintain confidentiality, the subjects will be identified only by numbers.

The completed eCRFs will be transferred to the Sponsor or designee. Copies of each eCRF will be retained by the PI. All source documents, records, and reports will be retained by the clinic.

All primary source data or copies thereof (e.g., laboratory records, eCRFs, data sheets, correspondence, photographs, and computer records) that are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report will be retained in the clinic archives.

Sponsor will inform the PI of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest (longest) standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or Sponsor standards/procedures; otherwise, the

retention period will default to the retention period of 15 years following completion of the clinical trial.

Blood and tissue samples will be collected and any remaining or back-up study samples may be used for future exploratory and biomarker analysis. The samples will be stored for up to 15 years.

9.1.8 Financing and Insurance

The financing and insurance for this study are outlined in the Clinical Trial Agreement.

9.1.9 Publication Policy

NGM will retain ownership of all data. All proposed publications based on this study will be subject to sponsor's approval requirements.

10 References

10.1 List of Sponsor's Clinical Studies Referenced in this Protocol

Study No.	Phase	Study Title	Study Population
Study 18-0501	1	A Phase 1, Multicenter, Open-Label, Single-Dose and Multiple-Dose Escalation Study of the Safety, Tolerability, and Pharmacokinetics of Intravitreal Injections of NGM621 in Patients with Geographic Atrophy Secondary to Age-related Macular Degeneration	Patients with Geographic Atrophy Secondary to Age-related Macular Degeneration

10.2 List of Sponsor's Nonclinical Studies Referenced in this Protocol

Study No.	Study Title
Study NGM621-TX-04	A 28-Week Repeat-Dose Toxicity Study of NGM621 in Cynomolgus Monkeys with a 12-Week Recovery Period

10.3 Literature References

Boyer DS, Schmidt-Erfurth U, van Lookeren Campagne M, et al. The pathophysiology of geographic atrophy secondary to age-related macular degeneration and the complement pathway as a therapeutic target. Retina. 2017 May;37:819–35.

Danis RP, Lavine JA, Domalpally A. Geographic atrophy in patients with advanced dry age-related macular degeneration: current challenges and future prospects. Clin Ophthalmol. 2015 Nov 20;9:2159–74.

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NCT02686658 ClinicalTrials.gov, Ophthotech Corporation. Zimura in subjects with geographic atrophy secondary to dry age-related macular degeneration [Internet]. 2019 [cited 2018 Aug 29]. Available from: https://clinicaltrials.gov/ct2/show/NCT02686658

Nussenblatt RB, Palestine AG, Chan CC, et al. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. Ophthalmology 1985;92:467–71.

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Sahu A, Lambris JD. Structure and biology of complement protein C3, a connecting link between innate and acquired immunity. Immunol Rev. 2001 Apr;180:35–48.

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11 Appendices

Appendix 1. Grading Scales

11.1 Grading Scale for Anterior Chamber Flare or Cells

Flare	
Grade	**Description**
0	None
1 +	Faint
2 +	Moderate (iris and lens details clear)
3 +	Marked (iris and lens details hazy)
4 +	Intense (fibrin or plastic aqueous)

Cells	
Grade	**Cells in Field [1]**
0	<1
0.5 +	1–5
1 +	6–15
2 +	16–25
3 +	26–50
4 +	> 50

[1]-Field size is a 1 mm by 1 mm slit beam

11.2 Grading Scale for Vitreous Cells

Cells	
Grade	**Cells per HPF**
0	0–1
Trace	2–20
1	21–50
2	51–100
3	101–250
4	>250
CG	Cannot grade
ND	Not done

11.3 Grading Scale for Vitreous Haze

Cells	
Grade	**Cells in Field [1]**
0	No inflammation
+0.5	Trace inflammation (slight blurring of the optic disc margins and/or loss of NFL reflex)
+1	Mild blurring of retinal vessels and optic nerve
+2	Moderate blurring of optic nerve head
+3	Marked blurring of optic nerve head
+4	Optic nerve head not visible

[1] *Discrete debris, such as from a PVD, is not included in the grading of inflammation. Avoid the impulse to grade debris as trace.*